

Computer-aided dosage in oral anticoagulation therapy using phenprocoumon

Problems and approaches

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Keywords

Oral anticoagulation, phenprocoumon, dosage, computer-aided expert system, mathematical models in anticoagulation therapy

Summary

Oral anticoagulation using vitamin K antagonists has been established for over 50 years. Although it is highly effective in preventing thromboembolic incidents, its therapeutic control still remains problematic. Therefore, a computer-aided approach is recommended for deriving dosages. Up to now, the dosage is often based on the visual inspection of previous INR measurements, average weekly doses, and the INR target range. Statistical variations of measurement results and time-delayed effects of dosages, however, frequently result in the misinterpretation of data and suggest pseudo-trends. Treating physicians are not only responsible for determining the patient-specific maintenance dose, but must also respond to deviating INR values,

overdosage or underdosage, initiate the oral anticoagulation therapy, and control the INR level in case of a new target range (bridging). Instructive examples are provided to illustrate the described difficulties.

A computer-aided expert system is currently developed to ensure the therapeutic safety under the specified conditions. We present preliminary results from a study designed to validate mathematical models underlying such expert systems.

Schlüsselwörter

Orale Antikoagulation, Phenprocoumon, Dosierung, computergestütztes Expertensystem, mathematische Modelle in der Antikoagulationstherapie

Zusammenfassung

Die orale Antikoagulation mit Vitamin-K-Antagonisten ist seit über 50 Jahren etabliert. Obgleich sie zur Verhinderung thromboembo-

lischer Ereignisse effektiv ist, ist ihre Therapiesteuerung problematisch. Ein computer-gesteuerter Lösungsansatz der Dosierung ist deshalb auch unter Berücksichtigung der demographischen Entwicklung wünschenswert. Bislang orientiert sich die Dosierung an INR-Messwerten, Wochendosen und dem INR-Zielbereich. Statistische Schwankungen von Messergebnissen und zeitverzögerte Auswirkungen von Dosierungen führen jedoch häufig zu Fehlinterpretationen und suggerieren Scheintrends. Neben der Ermittlung der patientenspezifischen Erhaltungsdosis stellen Über- bzw. Underdosierungen, die Initiierung einer oralen Antikoagulationstherapie und die terminorientierte Überbrückung im Rahmen operativer Eingriffe eine besondere Anforderung für Ärzte dar. Instructive Beispiele sollen für diese Probleme sensibilisieren. Ein rechnergestütztes Expertensystem liefert Lösungsansätze, um die Therapiesicherheit zu gewährleisten.

Ein solches Expertensystem basiert auf mathematischen Modellen, die den funktionellen Zusammenhang von Dosierung und Antikoagulationsniveau beschreiben. Wir präsentieren erste Ergebnisse einer Studie, mit deren Hilfe geeignete mathematische Modelle identifiziert werden sollen.

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Wege zur computergestützten Dosierung in der oralen Antikoagulationstherapie mit Phenprocoumon – Probleme und Lösungsansätze
Hämostaseologie 2010; 30: 183–189

If the INR values vary

- only slightly, oral anticoagulation using vitamin K antagonists, such as phenprocoumon (PPC), can be properly controlled by the physician and/or patient in anticoagulation self-management.
- considerably and there is a higher therapeutic target range, a declining main-

tenance dose, varying dosages, as well as interferences with existing co-medication, it is much more difficult to manage the therapy.

The complex cause and effect relationship makes it difficult even for experienced therapists to respond to the INR measure-

ments with suitable dosage recommendations.

Computer-aided analysis seems a wise method for responding to continuous high rates of hemorrhagic (up to 8 per 100 patient years) or thromboembolic complications (3 per 100 patient years) (1, 2, 10, 11, 13, 14). However, previous steps that

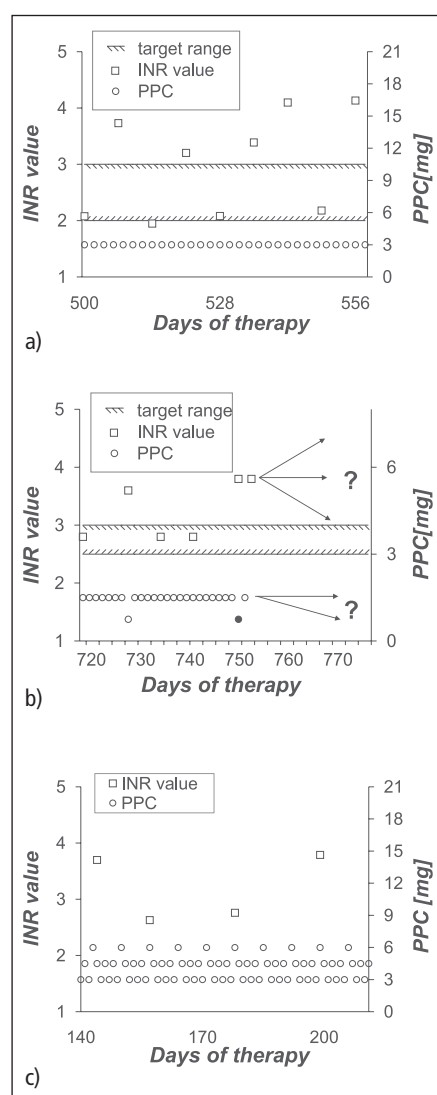


Fig. 1 INR value

a) variation despite constant PPC dose (data record 00268);

b) determination of the correction dose (●). Has the effect of the initial correction dose already abated after two days or not, and should a second correction dose be selected (data record 00245)?

c) Is the dispersion of the INR values caused by the varying daily dose that is administered within a constant weekly dose or which time behavior can be observed (diagram)?

have been taken to address this have not yet provided satisfying approaches (4, 5, 7, 9, 12).

Numerous examples are provided below that illustrate influencing factors, mutual dependencies, and erroneous interpretations of measurements. All this complicates the therapeutic control of the oral

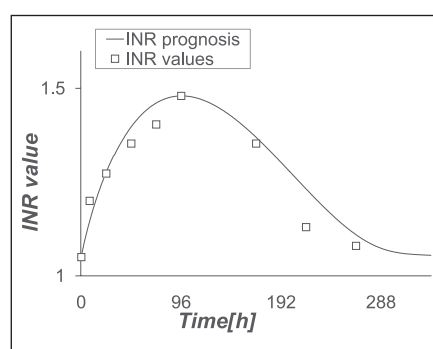


Fig. 2 INR deviation after a one-time dose of 12 mg PPC with the maximum value reached after 96 hours according to Haustein, Richter, and Vogel (8).

anticoagulation therapy using PPC. In conclusion, requirements for a computer-aided instrument are formulated from a medical perspective and approaches are outlined.

The core of such a computer-aided expert system is a mathematical model describing for each individual patient how INR values depend on dosage in the past. To assess models, a study was initiated. Preliminary results are presented in this paper.

Impaired therapy control with phenprocoumon

The attending physician or patient derives a recommended dose for the ensuing time period using information such as

- INR measurements,
- dosages, and
- the INR target range.

Although this method is straightforward, largely intuitive, and fast, it is characterized by subjective assessments and experience. This procedure harbors risks, since correlations that are difficult to assess are not taken into account. Such correlations are illustrated in the following examples.

Assessing measurement results

Statistical variations

INR measurements can vary considerably over the course of time (► Fig. 1) despite general conditions that (appear to) remain

constant and with a constant dose. The individual INR measurement is thus realization of a random variable. The greater the natural variation, the greater the risk when a prognosis and recommended dosage is derived from an inadequate number of INR measurements.

As it is, the physician/patients generally have access to treatment documentation that only contains tables and no graphs. To ensure that the assessment is easy to manage, the therapist often focuses on matching pairs, i. e. on past dosages that resulted in INR values within the target range. This further narrows the assessment basis for deriving a new recommended dosage and poses the risk of deducing inappropriate dosage recommendations.

Time-delayed effect of dosages

The observer tends to ascribe the INR measurements primarily to the dosages immediately before the measurement. However, the maximum effect of a dose is in fact reached after several days (8) (► Fig. 2).

An INR measurement in an ongoing treatment is a result of incidents that may have occurred several days ago (e. g. patient forgot to take a pill, special diet). If the dosage varies (► Fig. 1b and 1c), the measurement result depends on the temporal arrangement of the measuring interval within the dosing regimen. It must also be noted that the time-delay is patient-specific and the maximum effect of a one-time dosage is typically reached after 40–120 hours (6, 8). For these reasons, the effects of a change in dosage cannot be assessed until at least a few days later.

An intuitive interpretation of the measurement and rapid dosage adjustments can result in an even higher and dangerous INR variation.

Response to unexpected circumstances, over- and underdosage

In the event of dangerous deviations of the INR value, it is generally first assumed that the coagulation system will respond normally to the maintenance dose within a short period of time and that a correction dose is only required during the variation period.

Physicians frequently determine correction doses based on their experience. Due to the time-delayed effect of dosage changes (►Fig. 2), this can cause overreactions, which can even aggravate the situation.

A computer-aided prognostic analysis that is based on a patient-specific model can help to determine the appropriate response in such situations (►Fig. 1b).

Trends and pseudo-trends

If the response of a patient's coagulation system to the active agent changes, the maintenance dose may need to be changed. This particular situation can be identified, for example, if a suitable dosage administered in the past yields excessive (or insufficient) INR measurements with increasing frequency.

Since the INR measurements vary considerably even under unchanged circumstances, such a trend might be assumed based on a misinterpretation of the data (pseudo-trend). ►Figure 3a displays the data situation of a patient who goes to a medical practice for regular monthly control readings.

The INR values suggest a trend. In this data situation, the therapist has no choice but to respond by reducing the recommended dosage. There are also, in fact, weekly measurements for this patient. By including the weekly measurements (►Fig. 3b), the analysis surprisingly shows that there is no trend to be found at all, and that only the variation range has increased. The trend suggested by the data from Figure 3a turns out to be a pseudo-trend.

A computer-aided data analysis should therefore help differentiate between trends and pseudo-trends.

Risk patients and/or risk phases

Patients whose INR values frequently exhibit critical variations even under (apparently) constant circumstances are subject to increased risks. A matching profile with a constant dosage is displayed in ►Figure 4.

These risks must be addressed by taking INR monitoring measurements at

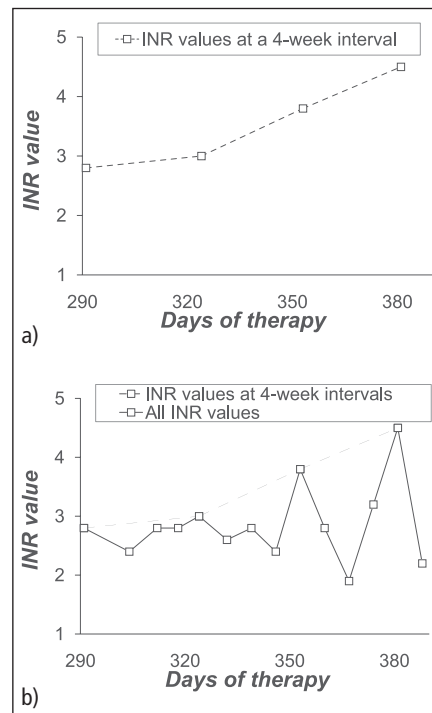


Fig. 3 Course of the INR value on the basis of **a)** measurement interval of four weeks with an upward trend (data record 00336); **b)** weekly INR values: The upward trend suggested by the monthly values (here as a dotted line) is a pseudo-trend (data record 00336).

short intervals. Formulating dosage recommendations for these patients using only a small number of INR measurements and without implementing controls at close intervals would pose a significant risk. Therefore, there is great interest in identifying risk patients at an early stage. A statistical data analysis based on a suitable computer-based model is required to accomplish this.

INR reduction based on target data

The anticoagulation therapy must occasionally be reduced or interrupted due to an upcoming surgical procedure. If the development of the INR values could be predicted by a computer-based patient specific model for the period of discontinuation/reduction, the door for an active INR management would be wide open. Risks for the patients by discontinu-

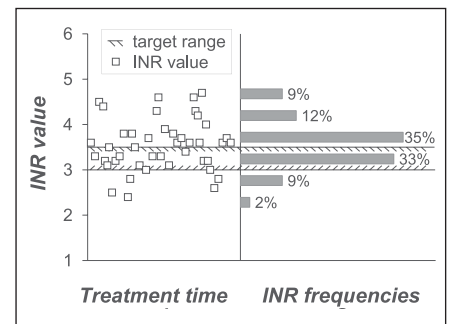


Fig. 4 Patient-specific INR frequency distribution (data record 00327).

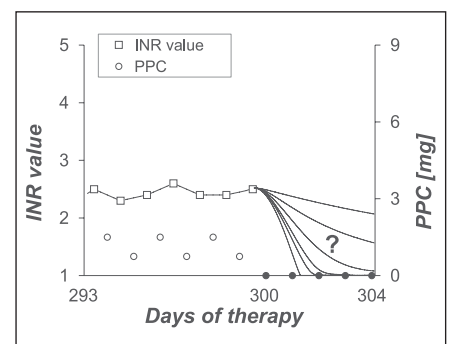


Fig. 5 Can the course of the INR reduction be calculated in advance after PPC has been discontinued (● zero-doses, diagram)?

ing the active ingredient for an extended period or by applying low-molecular-weight heparins (LMWH) for an unnecessarily long period (►Fig. 5) could be reduced significantly.

Patient-specific dosage

The core responsibilities of the therapist include providing patients with dosage recommendations. When prescribing a maintenance dose for an ongoing treatment, the therapist relies on the data from patients past treatment history. The therapist recommends the dosage that would presumably yield the desired anticoagulation level „under normal circumstances“ based on the patient's history. However, in reality, as described,

- the „natural“ variation range of the measurements must be taken into consideration,
- special effects must be deducted.

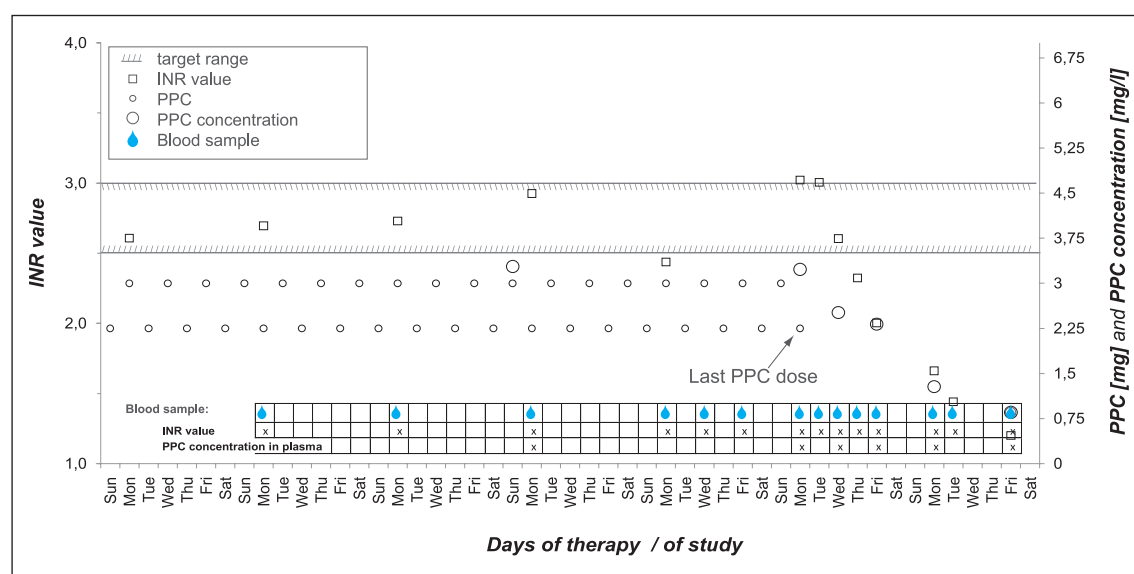


Fig. 6
Overview study
action

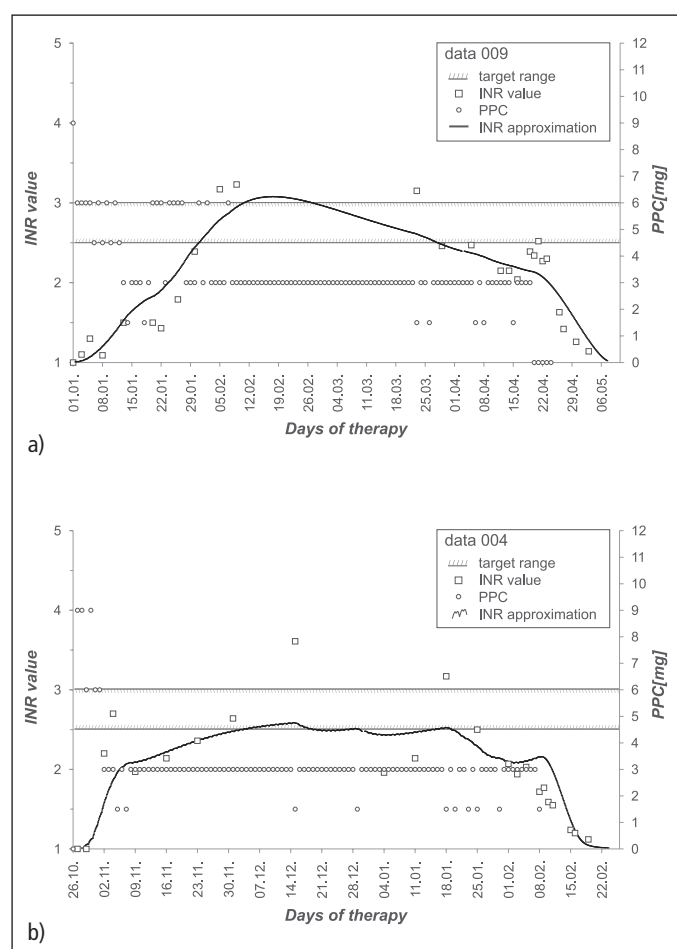


Fig. 7
INR measured values (□) and mathematical model (—) after identifying optimum model parameters from all measured values
a) patient 009: The model calculation displays very good compliance with the real treatment data.
b) patient 004: The model calculation displays good compliance with the real treatment data.

- The effect of
 - correction doses,
 - varying doses (► Fig. 1c),
 - time delays in the active system and
 - co-medication must be reflected.

This cannot be performed through a simple inspection, regardless of whether the data is represented in tables or is already prepared in graphs. Performing the above calculation requires the support of a computer-based expert system.

The time delay (► Fig. 2) has a particularly unpleasant effect during the initialization phase of the anticoagulation therapy: There is therefore a risk of detecting overdoses too late.

If, on the other hand, adequate measures are not taken in an appropriate timely manner, it takes an unreasonably long period until the INR target range is reached.

The series of INR measurements of the patient or a patient-specific model are not available at the beginning of the first initialization. In this case, a model based on the average patient used in combination with empirical values (3, 7) can yield an improved dosage recommendation, which can be increasingly adjusted to the patient-specific requirements once INR monitoring begins.

A patient-specific effect model would be very advantageous to determine a suitable initialization dosage when re-initializing

therapy following an interruption. This would allow the target state to be reached safely and as quickly as possible. During the first initialization and re-initialization phase, the situation can be further aggravated by aftereffects – which cannot always be easily assessed – from a previous heparin treatment.

Perspectives

It would be a great help for the treating physician if he was provided with support from a computer-aided expert system during therapy, in particular through assistance

- in determining the patient-specific maintenance dose,
- in preparing the therapy schedule depending on, for example, splitting pills into the smallest reasonable pieces, varying dosage, etc,
- with the response to potentially hazardous situations, e. g. by calculating the correction doses when exiting the therapy channel,
- with the INR reduction based on target dates (e. g. tooth extraction, elective hip-joint replacement),
- in identifying risk patients, and
- deriving simple basic rules in case the analytical instrument is not available.

In particular, a suitable analytical instrument must be able to calculate the patient-specific dosage, which yields a medically desirable/tolerable anticoagulation level. More specifically, the mathematical model must therefore

- take into consideration the dosage over an extended period (incl. varying dosage, forgotten dosages, etc.),
- reflect the patient-specific cause and effect correlation including time delay parameters,
- be able to identify „natural“ patient-specific variations and differentiate between short term special influences, as well as long term changes in patient-specific parameters,
- be adaptive to the individual patient and assess measurement data on the basis of such an individualized model, and

Fig. 8

Patient 009: The further course (—) can already be well forecasted over the short term, but not yet over the long term from the findings of only the first a) 6 INR values (—); b) 10 INR values.

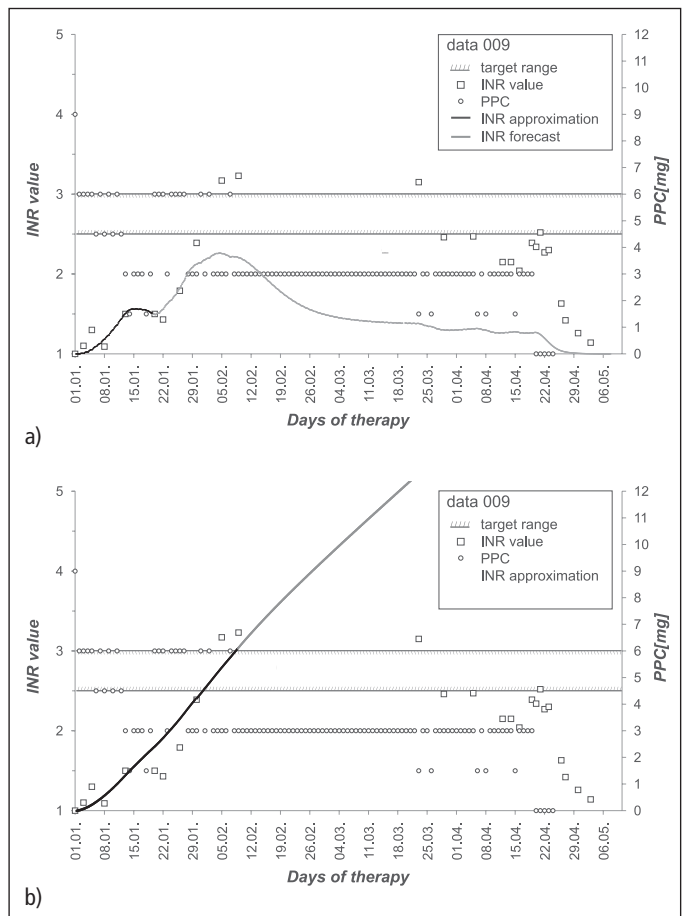
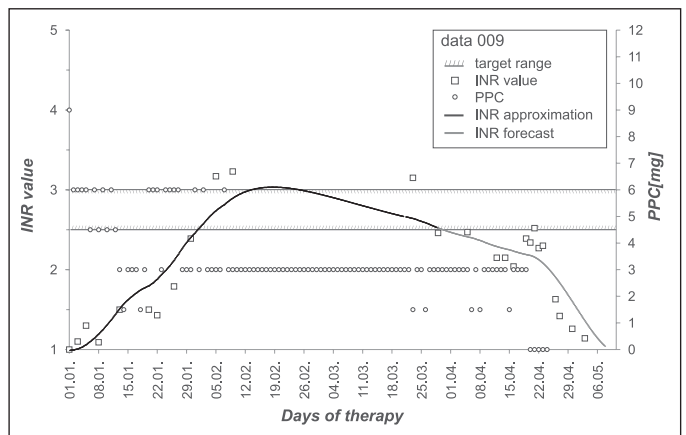


Fig. 9

Patient 009: The more INR values available, the more accurate the forecast of the further course.

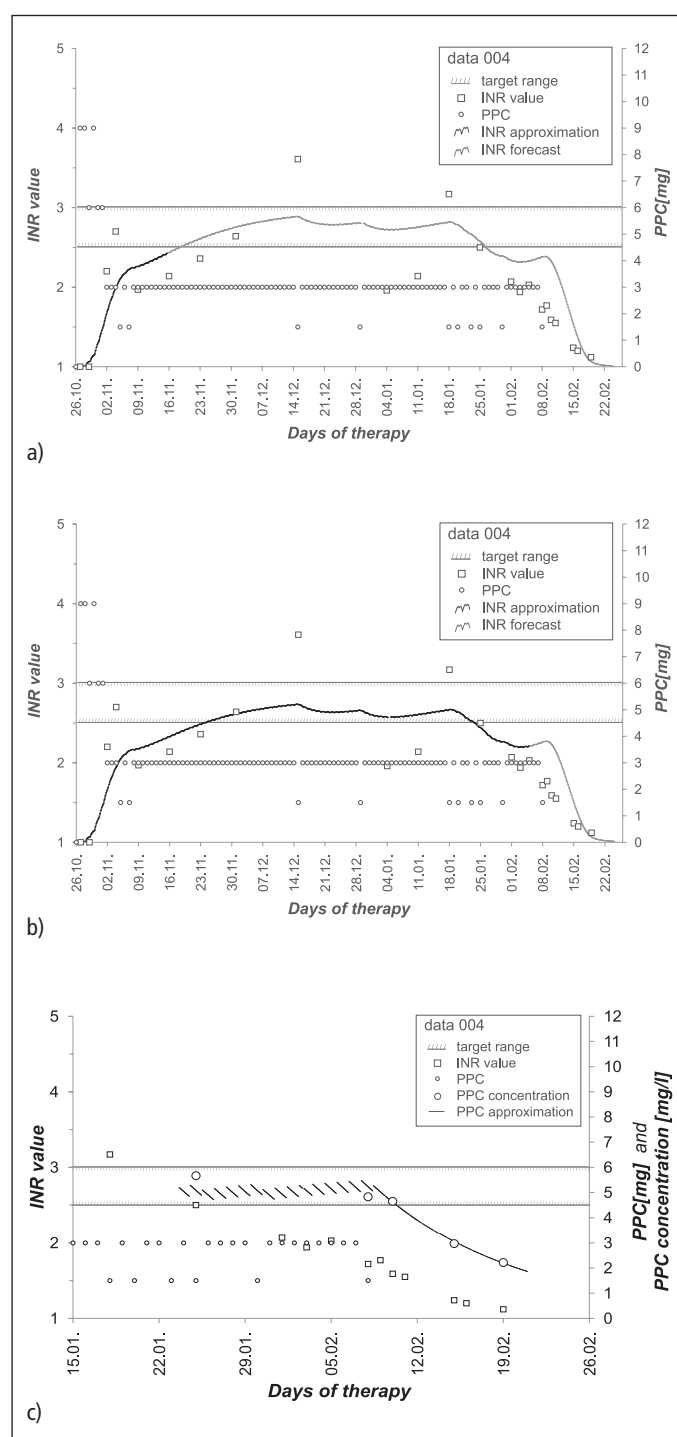


- integrate expert knowledge and extract simple basic rules.

The suitability of diverse approaches (linear, non-linear, control theoretic, differential equation approaches, etc.) is currently being examined.

Mathematical models in long term anticoagulation

The core of an expert system is the description of the functional dependence of the INR value on PPC dosages. The short term anomalous behavior should be dismissed,



since it is irrelevant for issues concerning the basic trend and maintenance doses, for example. Data was collected from 20 patients in an ongoing project to examine the suitability of various approaches. This also included a phase with a constant target channel as well as the discontinuation phase after PPC was discontinued.

Methods

A few key words about the methods employed to determine INR values and PPC concentrations; for more details the reader is referred to the subsequent final report: The Prothrombin Time PT (INR) was determined from citrate plasma

(3,2% citrate concentration) produced by centrifugation of citrated whole blood within 3 hours after drawing the blood. The INR was detected by the CL 8 (Behnk Elektronik GmbH, Hamburg, Germany), the thromboplastin Neoplastin (Roche, Mannheim, Germany) was used with an ISI of 1.18. The PPC concentration was determined by liquid chromatography/mass spectrometry according to the method described by Ufer M. et al (15).

The table in ►Figure 6 contains the times when (in a normal case) the most important measured values for the INR value, PPC dosage and PPC concentration were collected. The first analyses demonstrate that the examined function classes with adapted patient-specific parameters can generally represent the INR course as a function (►Figure 7a as an example for a stable patient and ►Figure 7b as an example for a patient with a higher portion of short term special influences).

For patients with known (separately determined) PPC decay rate λ_1 the *prognosis capacity* of the approach was tested. In this case, a mathematical *patient-specific* model for the functional dependence of the INR value on active ingredient doses was created from the doses and INR values up until time t_i . Prognoses for the INR values for the future times $t > t_i$ were prepared using this model and compared with the actual course starting from this time t_i .

Results

As expected, the prognosis quality improved as the amount of known patient data increased and the less short term special influences were present that affected the course (►Fig. 8a, b, ►Fig. 9 for a stable patient; ►Fig. 10a, b for a less stable patient).

The decay of a PPC concentration c_0 in the blood plasma can, as is generally known, be reliably represented through the function $c_0 e^{-\lambda_1 t}$ (6, 8).

λ_1 values around 0.1 mean that an initial concentration was only depleted by approximately 50% after 7 days. This once more strikingly demonstrates the effect of the time delay as described (►Fig. 10c).

A patient-specific functional represen-

Fig. 10

Patient 004

a) A good short term and sound long term prognosis of the further course is possible by using the knowledge gathered from the first 6 INR values;
b) With an increasing quantity of extracted treatment data (—) the self-learning mathematical model increases the accuracy of its INR prognosis (—) even further
c) PPC course $c(t) = c_0 e^{-\lambda_1 t}$ for patient 004 for $\lambda_1 = 0,083088107$. Using the extracted patient specifics and the applied daily doses, the course of the phenprocoumon concentration can be well reproduced. With this patient, a drop in the active ingredient concentration down approximately 50% from its initial level can be seen 7 days after the medication has been discontinued.

tation of the INR value depending on the dosage allows the following:

- A better distinction can be made between short term fluctuations of the INR level and the long term course.
- Effects of the active ingredient's time-delayed effect can be taken into account.
- Appropriate reactions can be determined for deviating situations.
- Long term trends can be distinguished from short term deviating situations.
- Patients with higher fluctuating rates can be identified.
- Forecasting discontinuation phases for treatment improves.
- The calculation of patient-specific maintenance dosages improves.

Conclusion

When determining a PPC dosage, the treating physician concentrates on the INR measurements, past PPC dosages, co-medication, etc. and tries to derive a suitable dosage for the future based on his experience and the assessment of the correlations. However, in light of the complex relationship, the effects of the influencing parameters in non-standard situations are difficult to assess, even for experienced therapists. A computer-aided expert system based on a suitable mathematical model may be a tremendous help. The examples and diagrams in this paper are designed to raise the reader's awareness of the hazards involved in a premature or perfunctory interpretation of INR measurements.

Preliminary results of a study comprising 20 patients demonstrate that the functional dependence of the INR values of past dosages can be displayed.

As the available data increase, the function classes observed adapt to a patient's specific conditions. They are suitable to

- determine patient-specific maintenance dosages,
- observe the time-delayed effect of dosages,
- distinguish between short term special developments and long term trends,
- calculate the effect of special dosages (high concentration doses), and
- react in a forward-looking manner to threatening deviating situations.

This model thus appears to be suitable to form the basis of an expert system.

Acknowledgement

We thank Else Kröner-Fresenius-Stiftung for generous support (Grant P 36/09: Mathematical models in oral long term anticoagulation therapy with phenprocoumon).

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