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Compliance-Guided Therapy

A New Insight Into the Potential Role of Clinical Pharmacologists

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Abstract

Background and objective: In the field of drug noncompliance, we investigated an original approach that could give the prescribing physician, in collaboration with a clinical pharmacologist, an active role. The aim here is for the prescribing physician to take compliance into account so as to provide an optimised prescription (choice of molecule prescribed and its rhythm of administration) adapted to each patient. The example considered is that of oral anticoagulant treatment prescribed long-term.

Methods: In order to investigate the choice of the best molecule and treatment regimen for a given noncompliance pattern, we performed an *in silico* study with two oral anticoagulant agents, warfarin and acenocoumarol, each taken in one or two daily doses. Three linked models were used: the first model generated specific noncompliance patterns, the second model described the pharmacokinetics of oral anticoagulant agents and the third model summarised the pharmacokinetic-pharmacodynamic relations.

Results: Considering different patterns of noncompliance (including timing errors in drug intake and the phenomenon of drug holidays) and comparing warfarin with acenocoumarol, we identified different situations in which one agent (prescribed once or twice daily) could clearly minimise both the thromboembolic and haemorrhagic risks. However, for some specific noncompliance patterns, the choice of the optimal therapy should also be guided by the basal individual thromboembolic and haemorrhagic risks.

Conclusion: Individualisation of drug therapy involves both drug dose and drug choice. In addition to the classical approach (i.e. drug level measurements, enzyme assays and even genetic sequence data), our study suggests that compliance-guided therapy may represent a potential, evolving way for the individualisation of prescriptions.

Background

In therapeutics, compliance is defined as the degree of coincidence between a person's behaviour and the prescription instructions given by his or her physician.[1] If consideration is restricted to strict drug compliance, then several patterns of noncompliance can be defined:[2] delay in the beginning and/or the termination of treatment, nonprescribed drug-

intake, omission of one or several doses, errors in the size of the dose taken, inappropriate timing and irregularity in administration. Overdosing, underdosing and erratic dosing intervals commonly occur in all populations, regardless of illness and of the drug.

According to the classical approach, any improvement in compliance to treatment implies a conscious effort on the part of the patient. The task of monitoring the regularity with which medication is taken, so as to reduce as much as possible the various patterns of noncompliance, is left up to the patient. Moreover, the roles of both the prescribing physician and drug labelling could be considered passive, providing advice and diverse recommendations in order to support and enhance compliance. More recently, and despite some limitations (unreliability in identifying the profiles of noncompliance, underestimation of compliance), patient questionnaires[3] have permitted certain patient characteristics to be identified that can be used to predict whether the patient will be a good or a poor complier. However, here again, the role of the prescriber is limited to an attitude of prevention, i.e. undertaking closer surveillance of patients likely to be poor compliers.

Electronic dosing boxes[4-7] have both modified the present day roles and relationships of patients, physicians and pharmacologists, and also greatly improved the research focused particularly on the pharmacometric implications of the recorded data. In clinical practice, these devices are used to identify poor compliance in nonresponding patients and those who completely fail to take their prescribed treatment. Up until now, the use of such devices as instructive tools has not been widely proposed; some investigators, however, have considered compliance monitoring in the clinical management of patients in the field of antihypertensive therapy.[8,9] Nevertheless, even under this scenario, any 'active' role for the prescriber remains very limited.

We wish to propose here an original approach that gives the prescribing physician, in collaboration with a clinical pharmacologist, an active role, involving the clinical pharmacologist directly in the choice of molecule prescribed and its rhythm of administration according to the individual noncompliance pattern of each patient. Even though this approach has not yet been clinically validated, the simulation given here illustrates its principal potential advantages. For the prescribing physician, the aim here is to take compliance into account, so as to provide an optimised prescription adapted to each patient. The example considered is that of oral anticoagulant treatment prescribed long-term in patients presenting, for example, with chronic atrial fibrillation. In relation to their narrow therapeutic index, oral anticoagulant agents may induce iatrogenic adverse events, with too low dosing leading to thromboembolic events and too high dosing being responsible for haemorrhagic complications.[10,11] In order to investigate the choice of the best molecule and treatment regimen for a given noncompliance pattern, we performed an *in silico* study with two oral anticoagulant agents, each taken in one or two daily doses.

Methods

The Global Approach

Three linked models were used: the first model generates specific noncompliance patterns, the second model describes the pharmacokinetics of oral anticoagulant agents and the third model summarises the pharmacokinetic-pharmacodynamic relations. Since the international normalised ratio (INR) is a widely used and reliable predictor of the efficacy and safety of oral anticoagulant treatments,[12] the output of these pharmacodynamic simulations were INR functions. Thus, for each time interval between two consecutive doses, we calculated the period over which the INR falls outside the commonly admitted target zone.

Compliance Models

With the advances in quantitative analytical methods and electronic technology, newer methods of compliance measurement have revealed drug-taking behaviour such as a pattern called 'drug holidays', where drug administration may be omitted for

Table I. Simulation of the four noncompliance patterns

Pattern	Distribution	Dosage interval (h)	
		mean	SD
1	Normal (for values $<0 \rightarrow \tau = 0.01$)	One dose/day: 24	12
		Two doses/day: 12	6
2	Normal (for values $<0 \rightarrow \tau = 0.01$)	From Monday to Friday:	
		one dose/day: 24	4
		two doses/day: 12	2
		From Friday to Monday:	
		one dose/day: 72	2
		two doses/day: 60	1
3	Transition matrix 0.1, 0.1, 0.8 0.2, 0.6, 0.2 0.1, 0.8, 0.1	One dose/day: 24	4
		Two doses/day: 12	2
4	Transition matrix 0.4, 0.0, 0.6 0.4, 0.6, 0.0 0.1, 0.8, 0.1	One dose/day: 24	4
		Two doses/day: 12	2

several days concurrently. Studies[13,14] have shown that patients were significantly more likely to miss a dose on a weekend and that there was significantly greater variability in the timing of weekend doses compared with weekday doses, or that the probability of missing a dose was significantly increased if the previous dose was also not taken.[13] In order to reflect these different drug-taking behaviours, two approaches were used for the noncompliance pattern simulations, and finally four patterns were generated.

In the first approach, consecutive dosage intervals (τ) were simulated following a normal distribution by varying the mean (e.g. 24 hours for a once-daily dose and 12 hours for a twice-daily dose) and standard deviation values. Two different poor or noncompliance patterns were then generated (table I). Pattern 1 simulates variable timing in dose intake, whereas pattern 2 simulates long periods without any dose intake, or drug holidays appearing, especially at the weekend. Negative values simulated with the normal distribution were truncated and replaced with an arbitrary value of 0.01 hours (in this way, double dose intake was also simulated).

For the second approach, making the assumption that any one dosing event depends on the occurrence of the previous dosing given the distribution of the dosing interval, a Markov model was used to describe compensation of missing dose and increased probability of missing a dose if the previous dose was also not taken.[13] The Markov regression was achieved using a matrix of probabilities and, depending on probability values within a matrix, two different patterns of poor or noncompliance were generated (i.e. noncompliance patterns 3 and 4, table I). The matrix expresses the drug-intake probability according to the previous drug-intake state. Each probability $P_{i \rightarrow j}$ corresponds to the probability of taking dose 'j' if the previous dose was 'i'. The variable 'drug intake' presents three different states: no dose (0), one dose (1) or a double dose (2) expressed in matrix line 1, 2 and 3, respectively. One matrix was defined as (equation 1):

$$\begin{bmatrix} P_{0\rightarrow0} & P_{0\rightarrow1} & P_{0\rightarrow2} \\ P_{1\rightarrow0} & P_{1\rightarrow1} & P_{1\rightarrow2} \\ P_{2\rightarrow0} & P_{2\rightarrow1} & P_{2\rightarrow2} \end{bmatrix} \text{ with } \begin{cases} P_{0\rightarrow0} + P_{0\rightarrow1} + P_{0\rightarrow2} = 1 \\ P_{1\rightarrow0} + P_{1\rightarrow1} + P_{1\rightarrow2} = 1 \\ P_{2\rightarrow0} + P_{2\rightarrow1} + P_{2\rightarrow2} = 1 \end{cases} \quad \text{(Eq. 1)}$$

The consecutive single dose, no dose or double dose generated in this way, was applied to the drug-intake interval with normal distribution parameters (e.g. 24 hours for a once-daily dose and 12 hours for a twice-daily dose).

Pharmacokinetic Models

The models involved a one-compartment pharmacokinetic model for warfarin[15] and a two-compartment pharmacokinetic model for acenocoumarol,[16] with absorption simplified as a bolus input assuming complete bioavailability (figure 1). The numerical values of the pharmacokinetic pa-

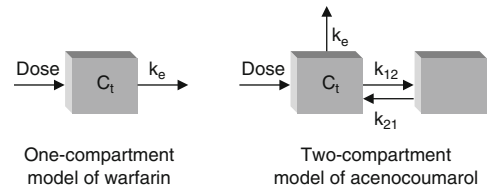

Fig. 1. Pharmacokinetic models for oral anticoagulant agents (warfarin and acenocoumarol). $\mathbf{C_t}$ = plasma drug concentration at a given time t; $\mathbf{k_{12}}$ = transfer rate constant (first-order) from the central (1) to a peripheral (2) compartment; $\mathbf{k_{21}}$ = transfer rate constant (first-order) from a peripheral (2) to the central (1) compartment; $\mathbf{k_e}$ = elimination rate constant.

Table II. Pharmacokinetic (PK) and pharmacodynamic (PD) model parameters for warfarin and acenocoumarol

Drug	PK parameters				PD parameters			
	V_d (L)[a]	k_{21} (h^{-1})	k_{12} (h^{-1})	k_e (h^{-1})	EC_{50}	k_d (h^{-1})	p_0	n
Warfarin	15	NA	NA	0.02	0.28	0.033	120	2
Acenocoumarol	17	0.103	0.0667	0.14	0.00538	0.04	120	1.15

a Bodyweight assumed as 70kg.

EC_{50} = the concentration that reduces the synthesis rate by 50%; **k_{12}** = transfer rate constant (first-order) from the central (1) to a peripheral (2) compartment; **k_{21}** = transfer rate constant (first-order) from a peripheral (2) to the central (1) compartment; **k_d** = apparent first-order degradation rate constant; **k_e** = elimination rate constant; **n** = shape parameter; **NA** = not applicable; **p_0** = prothrombin activity at baseline; **V_d** = volume of distribution.

rameters were chosen on the basis of bibliographic data[15-19] and are summarised in table II.

Pharmacokinetic-Pharmacodynamic Relationship

We used the physiological model proposed by Dayneka et al.[20] based on the fact that the pharmacodynamic response is determined by the balance between synthesis and degradation. The rate of change of the response over time with no drug present can be described by a differential equation. Since oral anticoagulants inhibit clotting factor synthesis, this relation incorporates a sigmoid maximum inhibition (I_{max}) model between concentration at a given time t (C_t) and the synthesis rate of the corresponding coagulation activity (prothrombin activity [p]). With p_0 corresponding to the baseline value of the effect without treatment (for $C_t = 0$), the differential equation is written as (equation 2):

$$\frac{dp}{dt} = k_d \left(\frac{p_0}{1 + \left(\frac{C_t}{EC_{50}} \right)^n} - p_t \right) \quad \text{(Eq. 2)}$$

This pharmacodynamic relation widely used for oral anticoagulant response modelling[16,21,22] involves three parameters: k_d, the apparent first-order degradation rate constant; EC_{50}, the concentration that reduces the synthesis rate by 50%; and n, a shape parameter. Finally, INR at a given time t (INR_t) was given by the ratio p_0/p_t, and p_t, the prothrombin activity at a given time t, was predicted by equation 2 using the pharmacodynamic parameters listed in table II.

Simulation Endpoint

For the four poor-compliance generated patterns, 6 months of treatment were simulated at an individual level for 30 patients. For each given pattern, the output of the simulations were the INR-time functions, i.e. INR_t, within each consecutive drug-intake interval which composed the 6-month treatment period. Then, the main calculated endpoint was the time during which the INR values were found to lie outside the target zone (i.e. <2 and >4.5). All simulations and calculations were carried out using Mathematica® software, 4th version (Wolfram Research, Inc., Champaign, IL, USA).

Statistical Analysis

A descriptive analysis was performed on INR results of the 6-month treatment period featuring poor compliance, without taking into account the preliminary 30-day treatment period (in order to begin the simulation at steady-state). For each non-compliance pattern, results are expressed as the mean time (± SD) during which INR values fell outside the target zone (i.e. <2 and >4.5).

Results

Noncompliance Patterns: 'Numerical Simulation Input'

Figure 2a shows a sequence of simulated times at which one patient ingests oral anticoagulant doses. Figure 2b describes for the simulated 30 patients the distribution of time intervals in hours between successive doses. Supposing the drug is prescribed once daily, the ideally compliant patient would generate a

regular pattern of one dose every 24 hours in figure 2a (see the first 30 days of therapy simulated to obtain the steady state and then excluded from the analysis) and, accordingly, all dose intervals of the same magnitude (24 hours) in figure 2b. An example of INR variation from day 28 to day 50 according to the noncompliance pattern of one patient is given in figure 3.

In noncompliance pattern 1 (figure 2a), intervals corresponding to the negative values (and then fixed at 0.01) appear as a double dose. Pattern 2 shows a bimodal distribution for the time intervals, the second mode corresponding to periods without any drug being taken over 3 days (e.g. a weekend). In patterns 3 and 4, we have considered in figure 2b that each $\tau > 80$ hours is equal to 80 hours, thus representing all the periods of no drug taking ≥80 hours. Patterns 3 and 4 show both drug holidays and the double dose phenomena.

International Normalised Ratio Functions: Numerical Simulation Output

Table III gives the average values (with the corresponding standard deviations) of the thromboembolic/haemorrhagic risk periods for the two oral anticoagulant molecules for each simulated noncompliance pattern and for one or two daily doses. For noncompliance pattern 1 (table III), one dose per day favours warfarin whereas two doses per day favours acenocoumarol (the difference of duration under the two oral anticoagulants for which INR is <2 not being clinically relevant). Finally, for pattern 1, the practical choice for an oral anticoagulant will be acenocoumarol (twice daily) in order to minimise

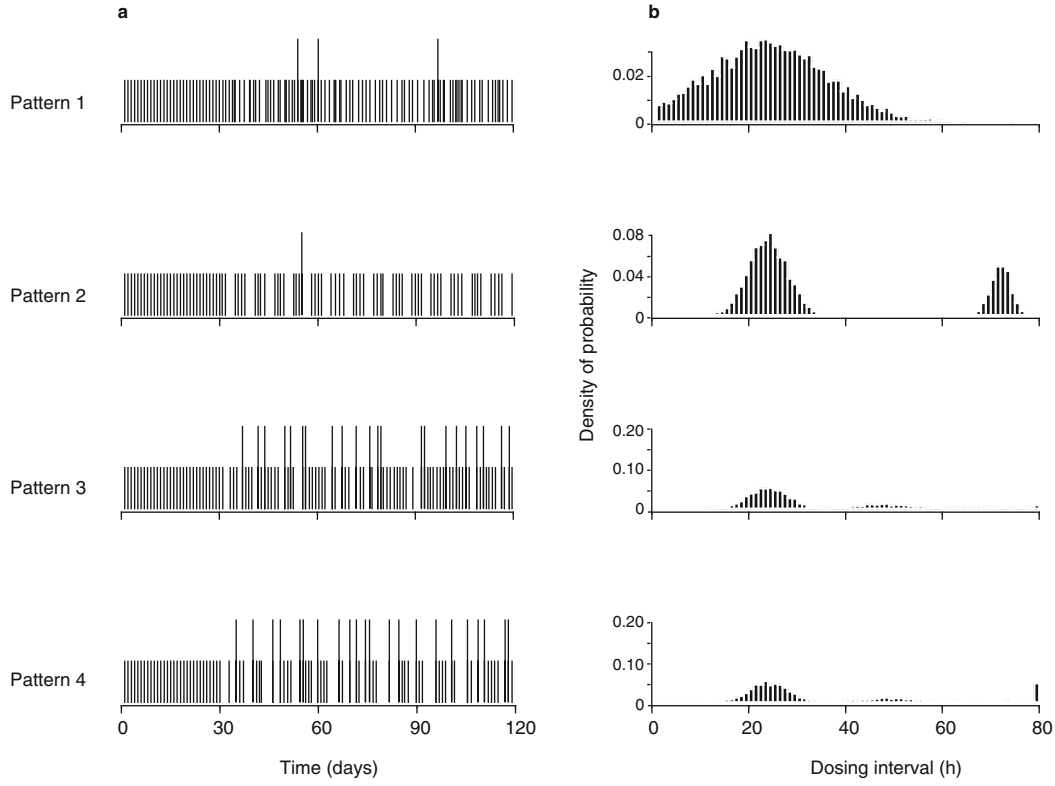

Fig. 2. Noncompliance patterns. (**a**) A sequence of simulated times at which one patient ingests oral anticoagulant doses. On the ordinate, each vertical line of unit height represents the taking of a single dose, and a line of two units high represents the taking of two doses. (**b**) Distribution of time intervals (hours) between successive doses.

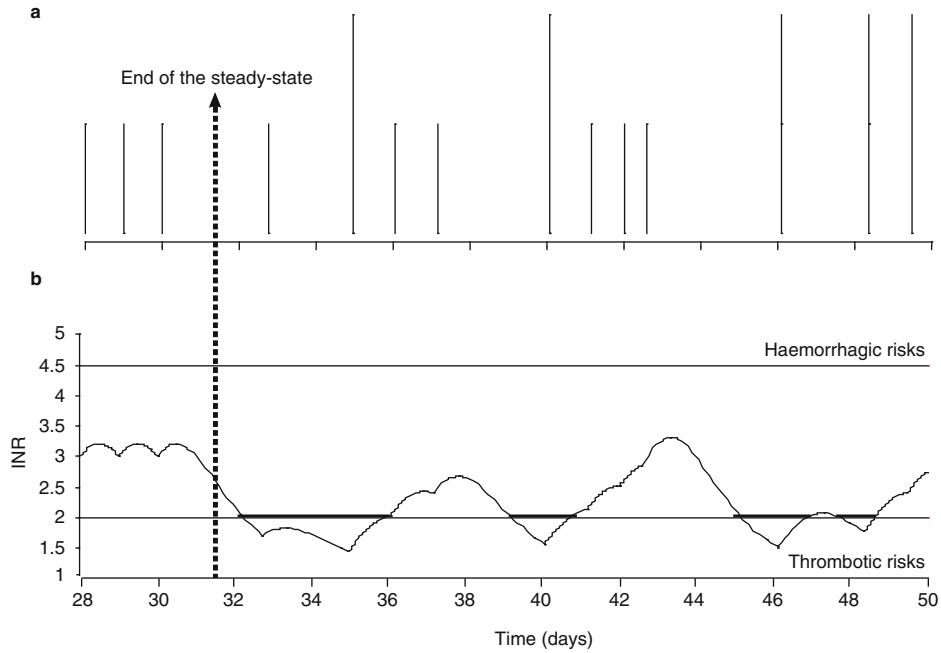

Fig. 3. (**a**) Example of a sequence of simulated times (from day 28 to day 50) at which one patient ingests oral anticoagulant doses. (**b**) Example of international normalised ratio (INR) variation from day 28 to day 50 according to the noncompliance pattern of the same patient. Line in bold shows the periods of time where INR values are outside the recommended therapeutic range (i.e. <2 and >4.5).

the duration of abnormal INR values. In the case of drug holidays (pattern 2, table III), the prescription of acenocoumarol (once daily rather than twice daily, in order to facilitate compliance) seems better. However, the practical choice in the case of pattern 3 (table III) must be discussed considering the spontaneous thromboembolic/haemorrhagic risks of the patient. For pattern 4 (table III), warfarin (twice daily) has to be preferred.

Warfarin decreases the thromboembolic risk (patterns 1, 3 and 4), but this advantage disappears in the case of long periods of drug holidays (pattern 2). In terms of haemorrhagic risks, warfarin (once daily) has a clinical advantage over acenocoumarol only in pattern 1. It appears that the kinetics of effect of warfarin can dampen the INR variations as a result of irregular timing in drug intake (pattern 1) or sporadic omission of one dose eventually compensated by a double dose (patterns 3 and 4). Nevertheless, in the case of drug holidays, the recovery of an adequate steady state is better obtained under acenocoumarol than with warfarin.

Discussion

The Example of Oral Anticoagulants

This example was chosen for several reasons. Firstly, the clinical benefit of oral anticoagulants in atrial fibrillation has been clearly established despite a narrow therapeutic index, which is unfortunately a cause of thromboembolic or haemorrhagic adverse events (in cases of under- or overdosing, respectively). Oral anticoagulant therapy significantly decreases the risk of stroke in patients with atrial fibrillation; this has been assessed in numerous clinical trials[23-32] and several meta-analyses.[33-36]

Secondly, the pharmacokinetic-pharmacodynamic relations of oral anticoagulants have been well established, but in view of their relative complexity, the exact relations between the characteristics of the pharmacokinetics, the pharmacokinetic-pharmacodynamic relations and the consequences of noncompliance in terms of clinical effect are, in practice,

difficult to interpret. Consequently, in such cases numerical simulation is compulsory.

Thirdly, the actual market offers various oral anticoagulant agents differing in their pharmacokinetic patterns, (i.e. a long elimination half-life for warfarin vs a short elimination half-life for acenocoumarol [40 vs 6 hours])[15,16] and these molecules can theoretically be taken as one or two daily doses.

The simulations performed in the present study demonstrate the possible impact of noncompliance on the pharmacodynamic effect (INR) of two oral anticoagulant agents with contrasting pharmacokinetics/pharmacodynamics used in long-term treatment. The simulated noncompliance patterns are characterised by variability in the timing of medication, the presence or absence of periods of variable duration without medication (drug holidays), and these being compensated for, or not, by a double dose. The main pharmacodynamic endpoint is highly correlated to the occurrence of clinical events,[12] and allows the thromboembolic (INR too low) and haemorrhagic (INR too high) risks to be estimated. However, the precise relations between the INR parameters and the probability of a given risk have not yet been elucidated.

The kinetics of warfarin smoothes the variations in INR due to irregular dosing (pattern 1), or to interspersed omitted doses whether compensated for or not by a double dose (patterns 3 and 4). These results are in agreement with the work of Laporte et al.[17] For warfarin, periods without medication (on average equal to 72 hours in pattern 2) give rise to longer periods over which the INR is <2 than for acenocoumarol. The regularity with which these periods without medication occur (often from the last dose on Friday to the first dose on Monday) do not enable a patient on warfarin to re-establish a satisfactory pharmacodynamic equilibrium during the rest of the week. In contrast, under acenocoumarol, effective and well tolerated INR values can be re-established more rapidly.

Table III. Noncompliance patterns and average durations of the thromboembolic/haemorrhagic risk periods under warfarin and acenocoumarol (n = 30 patients)[a]

Pattern	Duration (days): INR >4.5		Duration (days): INR <2	
	warfarin	acenocoumarol	warfarin	acenocoumarol
1[b]	**One dose/day: warfarin better**			
	12.4 ± 7.7	15.5 ± 5.4	6.2 ± 6.3	7.1 ± 3.5
	Two doses/day: acenocoumarol better			
	4.1 ± 2.6	1.3 ± 1.1	0.4 ± 0.8	0.8 ± 0.7
2[c]	**One dose/day: acenocoumarol better**			
	0	0.04 ± 0.15	151 ± 4.5	108.6 ± 1.6
	Two doses/day: acenocoumarol better			
	0	0	147 ± 3.8	109.5 ± 2
3[d]	**One dose/day: choice of molecule depending on the basal thromboembolic and haemorrhagic risks**			
	17.9 ± 7.4	11.9 ± 4	8.1 ± 4	23.3 ± 5
	Two doses/day: choice of molecule depending on the basal thromboembolic and haemorrhagic risks			
	11.6 ± 5	0.7 ± 0.85	0.9 ± 1.5	6.2 ± 2.7
4[e]	**One dose/day: warfarin better**			
	0.7 ± 0.9	0.9 ± 0.75	37.9 ± 9.5	51.7 ± 0.78
	Two doses/day: warfarin better			
	0.2 ± 0.7	0.04 ± 0.2	21.1 ± 0.85	35.7 ± 7.6

a Values are expressed as mean (± SD).

b Practical choice: acenocoumarol twice daily.

c Practical choice: acenocoumarol once daily.

d Practical choice: depending on the basal thromboembolic and haemorrhagic risks.

e Practical choice: warfarin twice daily.

INR = international normalised ratio.

Nevertheless, when acenocoumarol is preferred over warfarin, this work does not allow one to conclude that one rhythm of administration of acenocoumarol is superior to another. From a clinical point of view, two doses a day increase the risk of noncompliance. Additionally, the results of a study by Mismetti et al.[16] on real patients recommend the administration of acenocoumarol in a single daily dose.

Methodological Considerations

Noncompliance Models

The first stage of the noncompliance simulation was to distribute the time interval between each administration of medication according to a normal distribution law. This permitted several different scenarios to be investigated and the results to be explained relatively simply.[37] Markov patterns allow noncompliance to be simulated more realistically, but they are more difficult to interpret.[13] Nevertheless, one advantage of the Markov model is that it can capture the major features of noncompliance: this model of individual drug-taking behaviour posits an underlying habitual temporal pattern which is then disrupted by certain systematic and random departures from habit. These departures are (arbitrarily) decomposed in turn into two successive components, the first being departures from the habitual number of doses taken at each dosing time (i.e. one), and the second being departures from the habitual dosing times, given the number of doses to be taken at that time. This allows explicit recognition of the often observed fact that errors in dose timing are much more common than errors in dose taking. Lastly, the noncompliance patterns based on fractionated dose prescription often used for vitamin K antagonists, such as ¼, ¼ and ½, a quarter dose per day over 2 days followed by a half dose the third day and so on, could also have been simulated and studied.

Pharmacokinetic-Pharmacodynamic Models

Other pharmacokinetic-pharmacodynamic models could have been considered, such as a three-compartment model for the pharmacokinetics of acenocoumarol. Likewise, alternative methods of calculating the INR from the pharmacodynamic response could have been used, for example, a sigmoidal model used by Laporte et al.[17] One additional limitation of the present work is that we did not test the sensitivity of the parameters of the pharmacokinetic-pharmacodynamic models used for intersubject variations, and only the variations between individuals related to the noncompliance models were simulated. Further studies are necessary to test the robustness of our results considering the variability in the pharmacokinetic-pharmacodynamic parameters.

Display of Results

We chose the duration over which the INR is outside the fixed therapeutic targets of 2–4.5 as our principal outcome. This interval encompasses the target limits of the majority of indications for oral anticoagulant treatment.[38] This measure, highly correlated with the occurrence of clinical adverse events,[12] allows the thromboembolic (INR too low) or haemorrhagic (INR too high) risk to be evaluated. However, the precise relation between the INR parameter and the probability of the risk remains undetermined. Other parameters related to the INR (minimum and maximum amplitudes) could be calculated. One may think that too much variation over time in these parameters during the course of treatment could be harmful. All these parameters can provide information on the probability of a clinical event.[39-41] A logistic regression model could be added to link these intermediate outcomes (biomarkers) with a clinical outcome such as the probability of occurrence of a thromboembolic or an haemorrhagic event.

Implications for the Prescriber and Perspectives

Individualisation of drug therapy involves both drug dose and drug choice.[42,43] In addition to the classical approach (i.e. drug level measurements, enzyme assays and even genetic sequence data), monitored compliance-guided therapy may represent an additional way that drug therapy can be individualised. In the field of oral anticoagulant

agents, the choice between acenocoumarol and warfarin should depend not only on the patient's noncompliance pattern (as defined previously in the Methods section) but also on the thromboembolic or haemorrhagic risk that the patient presents depending on the pathology or its characteristics. Indeed, if the patient presents with a low thromboembolic risk *a priori*, one can give preference to a molecule that, according to the noncompliance pattern, minimises the occurrence of haemorrhages. In the opposite situation one must choose an oral anticoagulant agent that will reduce the periods in which the INR values are too low. Nonetheless, this approach can be envisaged only with prior knowledge of individual patient data on the values of the parameters required for the models and of the noncompliance pattern of each patient, assuming its stability over time. Lastly, for long-term treatments (years of therapy) the Markov model probably has to be made more sophisticated by incorporating time-varying covariates in order to describe the potential decrease of compliance over time. However, the robustness of such models over years of therapy remains unknown.

Conclusion

In the framework of evidence-based medicine, our work does not provide any clinical validation but only a theoretical modelling of potential benefits. It is only a preliminary exploration of how clinical pharmacological expertise might assist a clinician in addressing suboptimal adherence. A clinical validation would require a randomised clinical trial to be carried out comparing a control group of patients treated in the traditional way and a group receiving a treatment prescribed according to the noncompliance pattern assessed in advance in each patient, with a combination of thromboembolic events and bleeding as the outcome.

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