Stabilization of oral anticoagulant therapy in hospitalized patients and characteristics associated with lack of stabilization

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Abstract
The initiation and stabilization of oral anticoagulant therapy in hospitalized patients in a setting without specialized medical or pharmaceutical advice, was studied. In addition, potential risk factors for lack of stabilization were studied. All patients from three wards (orthopaedic surgery, general surgery and internal medicine) in two Dutch hospitals, who were started on oral anticoagulant therapy and who gave informed consent, were included in this three months prospective follow-up study. When a patient had two consecutive INR's within the range 2-3 during hospitalization (on day 6 or later), he was defined as stable. Stable and unstable patients were compared with respect to age, gender, quetelet index, length of hospital stay, indication for oral anticoagulant therapy, induction dosing schedule of oral anticoagulant therapy, prescribing physician, type of hospital (teaching or non-teaching), concurrently used drugs, concurrently used drugs known to potentially interact with oral anticoagulant therapy (drug-drug interactions that influence INR) and (co)morbidity. A total of 125 patients, who all used acenocoumarol as oral anticoagulant, were recruited in the study. The study population mainly comprised orthopaedic discharges on prophylactic oral anticoagulants. The mean length of hospital stay was 14.5 days (median 11.0, standard deviation (SD) 10.2) for the patients included in the study (patients with a short length of stay < 6 days were excluded from the study, because of the definition of stability). 43 patients (34%) became stable during hospitalization. The second INR within the range was reached after on average 11.1 days (median 10.0, SD 4.5).18 different induction dosing schedules were used. Differences in apparent risk of INR instability were statistically associated with length of hospital stay (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78-0.92), concurrent use of muscoloskeletal drugs, mainly NSAIDs, (OR 1.68, 95% CI 1.04-2.72) and two individual prescribing physicians (OR 6.61, 95% CI 1.47-29.82 for one physician and OR 0.23, 95% CI 0.06-0.99 for the other physician). This population has a high percentage of instability and reaches stability relatively late. The instability was associated with length of hospital stay, the concurrent use of musculoskeletal drugs (mostly NSAID's) and physician. Most of the unstable patients had INR's below therapeutic range, suggesting a conservative dosing habit. Part of the instability may also be due to the many different physicians who dose their own patients. Interventions to improve dosing may aid in better stabilization in hospitalized patients and thus in reduced length of hospital stay.

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Introduction

Oral anticoagulants have a narrow therapeutic window. Prothrombin times (reported as International Normalized Ratio, INR) outside the therapeutic range (2-3 for most indications, 3-4 for some indications [1]) are associated with either an increased risk of thrombo-embolic complications or an increased risk of bleeding [2,3]. Interactions with other drugs or with food as well as certain patient characteristics can lead to fluctuations in INR. Careful management of anticoagulant therapy is therefore essential.

Two models of anticoagulation management are generally used, namely routine medical care and coordinated care. In routine medical care anticoagulation is managed by the individual physician of the patient, whereas in the coordinated care model anticoagulation is managed by specialized anticoagulation clinics. The latter model has several advantages. Firstly, the clinics are staffed by healthcare professionals (physicians, nurses and/or pharmacists) who have much experience in managing oral anticoagulant therapy. Secondly, in many of these clinics tools (e.g. software) are available that can assist in dosing, in appointment scheduling and in the monitoring of drug-drug interactions. Studies have shown that management of anticoagulation in anticoagulation clinics is associated with a lower rate of complications [4].

In the Netherlands the coordinated care model is applied to outpatients, i.e. oral anticoagulant therapy is monitored in specialized anticoagulation clinics. However, oral anticoagulant therapy is most frequently initiated in hospitals. Management of in hospital anticoagulant therapy is normally not within the scope of these anticoagulation clinics, so in most Dutch hospitals the model of 'routine medical care' is applied. Anticoagulants are dosed by individual physicians, who are often part of the junior medical staff, lacking experience in dosing anticoagulants. This may have consequences for the stabilization of anticoagulant therapy. Therefore, a study was performed that looked into the stabilization of oral anticoagulant therapy in two Dutch hospitals. In addition, potential risk factors for lack of stabilization were studied.

Patients and methods

Setting

The study was performed in a teaching and a non-teaching hospital in the northern part of the Netherlands (Leeuwarden and Heerenveen), on three wards in each hospital (orthopaedic surgery, general surgery and internal medicine).

Population and sampling

For a total of three months in 1999 all consecutive patients on the specified wards, who were started on oral anticoagulant therapy and who gave informed

consent, were included. Excluded were those patients who did not stay in the hospital long enough to fulfill the criterion for stabilization of oral anticoagulant therapy, i.e. at least 6 days (see 'Study design'). Patients who used fenprocoumon in stead of acenocoumarol were also excluded.

Study design

This was a prospective, observational follow-up study. For all included patients several characteristics were determined: age, gender, quetelet index (=bodyweight (in kg)/(length (in m))^2; the quetelet index is an indicator for obesity), indication for oral anticoagulant therapy, concurrently used drugs (from the records of the hospital pharmacies), comorbidity (from the patient record), type of hospital (teaching or non-teaching) and length of hospital stay. With respect to anticoagulant therapy, the following parameters were collected from the medical record: prescribing physician, day of therapy (day 1 is day of first dose), induction dosing schedules (i.e. dose of anticoagulant on day 1 and day 2), dose for every other day of therapy and INR (all measured values, not necessarily on each day of therapy). Potential complications (thrombo-embolic events and bleeding episodes) were obtained from the medical record as well. In both hospitals INR is measured at least once every three days for each patient until stabilization of oral anticoagulant therapy. Thereafter, INR's are measured less frequently.

The therapeutic range for the INR's was set at 2-3, as there were no patients who needed the higher range of 3-4. A patient was defined as stable, in case he or she had two consecutive INR's within this range during hospitalization with the first (of the two consecutive INR's within range) having been measured on day 5 or later. In the same way instability was defined as the lack of two consecutive INR's within the range, during hospitalization. From this criterion it follows that patients had to stay in the hospital for at least 6 days in order to be included (see 'Patients').

For patients with stabilization during hospital stay, the time to stabilization was determined. This was defined as the time that elapsed from day 1 of oral anticoagulant therapy to the day, when the second consecutive INR was within range.

Stable and unstable patients were compared with respect to age, gender, quetelet index, type of hospital, length of hospital stay, indication for oral anticoagulant therapy, induction dosing schedule of oral anticoagulant therapy, prescribing physician, concurrently used drugs, concurrently used drugs known to potentially interact with oral anticoagulant therapy (drug-drug interactions that influence INR) and comorbidity. Physicians were aware of the study. The study was approved by the medical ethics committees of the two hospitals.

Data analysis

The concurrently used drugs were classified according to the ATC (Anatomical Therapeutic Chemical) code [5]. The data were analyzed using Statistical Package for Social Sciences (SPSS) version 9.0. Pearson Chi-Square test was used to compare the frequency of INR's beneath, within and above therapeutic range (from day 5 and later) between stable and unstable patients. Using univariate logistic regression analysis the associations between lack of stabilization and age, gender, quetelet index, length of hospital stay, concurrently used drug classes (five most prescribed classes), concurrently used drugs known to potentially interact with oral anticoagulant therapy (influence INR), comorbidity (five comorbid states with highest occurrence rate), indication for oral anticoagulation, initial dosing scheme of oral anticoagulant therapy (five mostly used schemes), type of hospital and prescribing physician (five top prescribers) were determined. Regression analysis was used, because data on many variables were obtained in this study and in general it is preferable to use advanced statistical methods that analyse all variables in stead of using a series of simple analyses. As the outcome variable (stability or instability) is binary, logistic regression analysis was used.

Results

The analyzed study population consisted of 89 female and 36 male patients, after exclusion of 3 patients because they used fenprocoumon and exclusion of 2 patients because of a hospital stay of less than 6 days. The general characteristics of the study population are summarized in table 1. 67% of patients (n=84) received oral anticoagulant therapy after orthopaedic surgery. The mean length of hospital stay was 14.5 days (median 11.0, SD 10.2, range 6-66 days). A total of 18 different induction dosing schedules were used in the two hospitals but 5 schemes accounted for the majority of patients (n=101, 81%). These schemes were prescribed by 16 different physicians of whom 5 accounted for 94 patients (75%). One third of all patients (n=41) were treated in the teaching hospital. The five most commonly occurring comorbidities, as well as the five classes of drugs that were most commonly used as concurrent medication can be seen in table 1. Of all concurrently used drugs 5% was known to potentially interact with oral anticoagulant therapy (n=39).

43 patients (34%) were considered as stable during hospitalization. The second INR within the range was reached after on average 11.1 days (median 10.0, SD 4.5, range 6-25 days). Between two consecutive INR's a maximum interval of 3 days elapsed.

Table 2 shows the distribution of INR's, measured on day 5 or later (below, within or above therapeutic range), for stable and unstable patients. The unstable patients have a larger number of INR-values below therapeutic range (Pearson's Chi-square $p<0.0005$).

Table 3 shows the association between lack of stabilization and the characteristics age, gender, quetelet index, length of hospital stay, concurrently used drug classes, concurrently used drugs known to potentially interact with oral anticoagulant therapy, indication for oral anticoagulation and type of hospital, as well as their 95% confidence intervals.

The five most commonly occurring comorbidities and the five dosing-schedules used most often are not included in table 3. They were not associated with lack of stabilization.

Length of hospital stay shows an inverse association with instability (odds ratio (OR) 0.85, 95% confidence interval (CI) 0.78-0.92) and the concurrent use of musculoskeletal drugs is associated with instability (OR 1.68, 95% CI 1.04-2.72). Although not included

Table 1 *General characteristics of study population (n=125)*

Characteristic	*n (%)*	*Mean*	*st.dev.*	*Range*
Age (years)	-	72.0	12.0	19-97
Quetelet index (kg/m^2)	-	27.2	4.2	17.6-49.6
Concurrently used drug classes[a]				
• blood	143 (19)	-	-	-
• cardiovascular	118 (16)	-	-	-
• central nervous system	106 (14)	-	-	-
• antimicrobials	105 (14)	-	-	-
• musculoskeletal	92 (13)	-	-	-
Concurrently used drug known to potentially interact with oral anticoagulant therapy	39 (5)	-	-	-
Comorbidity[b]				
• hypertension	28 (13)	-	-	-
• diabetes mellitus II	14 (6)	-	-	-
• asthma and COPD	10 (5)	-	-	-
• previous thromboembolism	10 (5)	-	-	-
• edema	7 (3)	-	-	-

[a] In total 736 drugs were used by the 125 patients; drug classes:
- blood = drugs acting on the blood, e.g. anticoagulants, iron salts, plasma expanders
- cardiovascular = cardiovascular drugs, e.g. antihypertensive drugs, drugs used in heart failure, drugs used in angina pectoris, lipidlowering agents
- central nervous system = drugs acting on the central nervous system, e.g. opioid analgesics and other analgesics (with the exclusion of NSAID's), antidepressants, antipsychotics
- antimicrobials = antibacterial and antiviral drugs, drugs against parasites
- musculoskeletal = drugs acting on the musculoskeletal system, e.g. NSAID's, muscle relaxants, bisfosfonates

[b] In total 219 comorbidities were recorded for the 125 patients.

Table 2 *Distribution of INR's from day 5 and later (below, within or above therapeutic range), for stable and unstable patients*

	stable[a] (%)	unstable (%)
below	59 (22)	133 (59)
within	151 (55)	48 (21)
above	62 (23)	45 (20)

Pearson Chi-Square $p < 0.0005$

[a]Patient defined as stable, in case he or she had two consecutive INR's of 2-3 during hospitalization with the first (of the two consecutive INR's within range) having been measured on day 5 or later

in table 3, the association between instability and the individual prescribing physicians was also analysed. There was a statistically significant association between instability and two individual physicians (OR 6.61, 95% CI 1.47-29.82 for one physician and OR 0.23, 95% CI 0.06-0.99 for the other physician).

No clinically relevant complications of oral anticoagulant therapy (neither bleeding episodes nor thrombo-embolic events) were found in patient records during the study.

Discussion

In this study 43 patients (34%) became stable during hospitalization. The second INR within the range was reached after on average 11 days. In literature percentages for in hospital stabilization (using physician dosing) are found to be 100% [6] and 56% [7]. Patients reach stability after a mean (sometimes median) of 8.4 [7], 9.4 [8], 9 [9] or 10.3 [10] days. In all of these studies warfarin is used as an oral anticoagulant, while in this study acenocoumarol is used. Theoretically, the stabilization on warfarin therapy should be equal to or perhaps slower than the stabilization on acenocoumarol, as the maximum effect after a first dose of warfarin is reached after 36-72 hours and that of acenocoumarol after 36-48 hours [11].

The included patients differ from the population in our study. The mentioned studies [6-10] mostly included patients who were started on oral anticoagulation because of therapeutic indications, while most of the patients in this study were treated with prophylactic oral anticoagulant therapy. It seems likely that physicians tend to dose conservatively in a prophylactic setting and indeed most INRs outside the therapeutic range were below the therapeutic index. However, Sun et al. found that physicians dose conservatively for therapeutic indications as well [12]. As it is important to reach therapeutic INR's in a prophylactic setting, the instability found in our study is undesirable. Furthermore, as the physicians were aware of being in the study, the situation in real life may be even worse.

When comparing all these studies to ours, it seems that our population had a lower level of stabilization and reached stable INR's later. From the logistic regression model the only variables clearly associated with instability are length of hospital stay, concurrent

Table 3 *Association of instability (not having two consecutive INR's of 2-3 during hospitalization) with the characteristics age, gender, quetelet index, length of hospital stay, concurrently used drug classes, concurrently used drug known to potentially interact with oral anticoagulant therapy, indication for oral anticoagulant therapy and type of hospital*

Characteristic	*OR[1] (95% CI[2])*
Patient characteristics	
age	0.97 (0.93-1.00)
gender (female)	0.94 (0.41-2.12)
quetelet index	1.08 (0.95-1.21)
length of hospital stay	0.85 (0.78-0.92)
Drug characteristics	
Drug classes of concurrently used drugs[3]	
• blood	1.30 (0.88-1.91)
• cardiovascular	0.89 (0.60-1.34)
• central nervous system	0.86 (0.57-1.31)
• antimicrobials	1.43 (0.92-2.23)
• musculoskeletal	1.68 (1.04-2.72)
Concurrently used drug known to potentially interact with oral anticoagulant therapy	0.72 (0.37-1.37)
Indication for oral anticoagulant (orthopaedic)	0.98 (0.45-2.16)
Physician characteristics	
Type of hospital (teaching)	0.63 (0.29-1.37)

[1] OR = Odds Ratio
[2] CI = Confidence Interval
[3] Reference category consists of all other values, e.g. the reference category for drug class 'blood' is non-blood drugs

use of musculoskeletal drugs (mostly NSAID's) and two physicians. Type of hospital was not associated with instability, although one might expect that instability is more likely to occur in teaching hospitals. In teaching hospitals oral anticoagulants are often dosed by relatively inexperienced junior physicians. Furthermore, no association was found between instability and concurrently used drugs known to potentially interact with oral anticoagulant therapy. Possible explanations for this surprising finding are: relatively few interacting drugs were used in this study (5% of all concurrently used drugs), physicians take drug-drug interactions into consideration when dosing oral anticoagulants and drug-drug interactions found in literature are not always clinically relevant.

The small inverse association of instability with length of hospital stay may be explained by the fact that a longer duration of hospital stay increases the likelihood of being stabilized on oral anticoagulant therapy. However, it may also simply be a reflection of the effect of the patient's general clinical instability on INR stabilisation. The association between the use of musculoskeletal drugs (mostly NSAIDs) and instability may be explained by conservative dosing. As NSAIDs increase bleeding time, physicians may tend to dose coumarins more carefully. A substantial part of INR's was below therapeutic range in our study, so this conservatism indeed seems to add to instability. This study population was hospitalized for an average of 14.5 days, which may in part have been due to the instability of oral anticoagulation. Nevertheless, the proportion of patients leaving the hospital without evidence of stabilisation is relatively high, so the physicians in this prophylactic setting may find it unnecessary for INR to be stabilized during hospitalization.

The instability could not be explained by the logistic regression model, but may be explained by the many different physicians who dose their own patients, each physician in his own way, without using dosing tools (such as nomograms or computers).

In this study population no clinically relevant complications of oral anticoagulant therapy were detected, which may be caused by the relatively small population studied. Most patients had INR's below the therapeutic range, which made bleeding complications even more unlikely to be found.

Some remarks can be made about this study. Firstly, the applied criterion for stability of oral anticoagulant therapy was less strict than in other studies [7,9]. By using a more strict criterion, the instability would even be larger in this study, so this would not alter the conlusion. Secondly, not all possible variables have been included in the logistic regression model. For example, the influence of food was not studied. Thirdly, one could argue that the small proportion of stable patients may be the result from one inadequately dosing physician. However, when the physician with the highest degree of instable patients is excluded from analysis, the proportion of stable patients is 40%, which still is much lower than in other studies [6,7]. A final limitation of this study is that it concerns only two Dutch hospitals. Whether the results are applicable to other Dutch hospitals should be subject of future studies.

Notwithstanding these limitations, this study shows that stabilization of oral anticoagulant therapy during hospitalization is poor. Several studies have shown, that in hospital stabilization may be improved by the introduction of nomograms or computerized dosing [6-10 12]. Furthermore, the coordinated care

model [4] used for outpatients could be introduced in Dutch hospitals and this may aid in better stabilization. Better stabilization may result in shorter length of hospital stay and may thus be of value, both with respect to patient care and to economic aspects.

Conclusion

Our study population had a high percentage of instability and reached stability relatively late.

The instability was associated with length of hospital stay, the concurrent use of musculoskeletal drugs (mostly NSAID's) and physician. Most of the unstable patients had INR's below therapeutic range, suggesting a conservative dosing habit. Not less than 18 different induction dosing schedules were used, so part of the instability may also be due to the many different physicians who dose their own patients. Therefore, interventions to improve dosing (e.g. by using computers) or transferring the responsibility for dosing from non-specialized physicians to a specialized anticoagulation clinic may aid in better stabilization in hospitalized patients. In turn, better stabilization could result in shorter length of hospital stay and thus in cost savings and better patient care.

References

1 Haemostasis and Thrombosis Task Force for the British Committee for Standards in Haematology. Guidelines on oral anticoagulation: third edition. Br J Haematol 1998;101:374-87.

2 Fihn SD, McDonell M, Martin D, Henikoff J, Vermes D, Kent D, et al. for the Warfarin Optimized Outpatient Follow-up Study Group. Risk factors for complications of chronic anticoagulation. A multicenter study. Ann Intern Med 1993; 118:511-20.

3 Gulløv AL, Koefoed BG, Petersen P. Bleeding during warfarin and aspirin therapy in patients with atrial fibrillation. The AFASAK 2 study. Arch Intern Med 1999;159:1322-8.

4 Ansell JE. Anticoagulation management as a risk factor for adverse events: Grounds for improvement. J Thrombosis Thrombolysis 1998;5:S13-S18.

5 Anonymous. Anatomical Therapeutic Chemical (ATC) classification index. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 1994.

6 Fennerty A, Dolben J, Thomas P, Backhouse G, Bentley DP, Campbell IA, et al. Flexible induction dose regimen for warfarin and prediction of maintenance dose. BMJ 1984;288:1268-70.

7 Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. Clin Pharm 1987;6:37-45.

8 White RH, Hong R, Venook AP, Daschbach MM, Murray W, Mungall DR, et al. Initiation of warfarin therapy: comparison of physician dosing with computer-assisted dosing. J Gen Intern Med 1987;2:141-8.

9 Vadher B, Patterson DLH, Leaning M. Evaluation of a decision support system for initiation and control of oral anticoagulation in a randomised trial. BMJ 1997;314:1252-6.

10 Kovacs MJ, Cruickshank M, Wells PS, Kim H, Chin-Yee I, Morrow B, et al. Randomized assessment of a warfarin nomogram for initial oral anticoagulation after venous thromboembolic disease. Haemostasis 1998;28:62-9.

11 Anonymus. Cumarinederivaten. In: Informatorium Medicamentorum 2000. 's Gravenhage: Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie, 2000:299.

12 Sun J, Chang MW. Initialization of warfarin dosages using computer modeling. Arch Phys Med Rehabil 1995;76:453-6.