Identification of Factors Responsible for Oral Over-Anticoagulation in Outpatients with Heart Disease

Román Freixa, Pedro Blanch, Montse Ibernon, Jaume Padró, Javier Delso, José Luis Sobrequera, Elena Salas, Laura Dos, and Pere Codinach


Background. Few studies have attempted to investigate the clinical course or identify factors responsible for excessive anticoagulation in patients with heart disease.

Objectives. To determine the incidence of excessive anticoagulation in outpatients with heart disease treated with acenocoumarol, analyze the factors related with over-anticoagulation, and identify bleeding complications.

Patients and method. This 7-month prospective observational study included consecutive outpatients anticoagulated with acenocoumarol. They were seen in an anticoagulation unit. The high INR group of 55 over-anticoagulated patients had at least one test with INR > 5. The control group of 49 patients had INR results strictly within therapeutic range.

Results. A total of 3,683 INR determinations were made in 512 patients. Seventy-seven tests had an INR > 5 (a 2% overall incidence of high-INR). In the group of 55 INR < 5 patients, 31% had more than one INR determination > 5 during follow-up. Multivariate analysis identified four variables as independent predictors of over-anticoagulation: artificial heart valve, poor treatment compliance, addition of potentially interactive new drugs, and illness in the last month. The high-INR group patients had more bleeding episodes (21.8 vs 4.08%; p = 0.008), one of which was major.

Conclusion. The incidence of excessive oral anticoagulation in our outpatient population was similar to that reported in other studies. Patients with INR > 5 had more total bleeding complications, mostly minor. It is recommended to proceed carefully with oral anticoagulant therapy in patients with an artificial heart valve, suspected poor treatment compliance, addition of potentially interactive new drugs, and illness in the last month.

Key words: Anticoagulants. Patients. Test.

Identificación de factores responsables de anticoagulación oral excesiva en pacientes ambulatorios con cardiopatía

Correspondence: Dr. D. Román Freixa.
Servicio de Cardiología. Hospital Creu Roja.
D. de Maig, 301. 08025 Barcelona. España.
E-mail: roman.freixa@consorcicreuroja.es

Received 4 February 2002.
Accepted for publication 19 August 2002.

Background. Pocos estudios han examinado la evolución clínica o la identificación de los factores responsables del mal control de pacientes con cardiopatía que han recibido tratamiento anticoagulante.

Objetivos. Determinar la incidencia de enfermos con un exceso de anticoagulación en una población de pacientes con cardiopatía tratados con dicumarínicos, analizar los factores relacionados con esta sobredosificación e identificar las complicaciones hemorrágicas.

Pacientes y método. Se trata de un estudio observational y prospectivo en pacientes con cardiopatía anticoagulados con acenocoumarol, controlados ambulatoriamente y con un periodo de seguimiento de 7 meses. Incluía un grupo de estudio (n = 55), pacientes excesivamente anticoagulados (INR > 5), y un grupo control (n = 49): pacientes con INR estrictamente dentro del intervalo terapéutico.

Resultados. Se realizaron 3.683 determinaciones de INR en 512 pacientes. Se identificaron 77 tests con INR > 5, que corresponden al 2% del total. En total fueron 55 pacientes con INR > 5, y el 31% de ellos (17 pacientes) tuvo más de un test > 5 durante el período de estudio. El análisis multivariado identificó 4 variables predictoras independientes de excesiva anticoagulación: pacientes portadores de prótesis valvular mecánica, mal cumplimiento terapéutico, adición de nuevos fármacos con interferencia y enfermedad intercurrente en el último mes. Los pacientes con INR > 5 presentaron más hemorragias totales (21,8 frente a 4,08%; p = 0,008). Sólo un paciente sufrió una hemorragia mayor.

Conclusiones. La incidencia de excesiva anticoagulación en pacientes con cardiopatía controlados de modo ambulatorio es aceptable. Los pacientes con INR > 5 presentan una incidencia más elevada de hemorragias totales, la mayoría de las cuales es menor. Debe tenerse especial precaución cuando se realiza tratamiento anticoagulante a pacientes portadores de prótesis mecánicas, con nuevos fármacos añadidos que interfieran con la anticoagulación, con enfermedad intercurrente en el último mes y si hay sospecha de que exista un incorrecto cumplimiento.

Palabras clave: Anticoagulantes. Pacientes. Test.
INTRODUCTION AND OBJECTIVES

Oral anticoagulants are widely prescribed in patients with heart disease. The ideal conditions for using this medication, among others, are a predictable effect-dose and individualized maintenance dose. However, no oral anticoagulant meets these conditions. These drugs are characterized by a dose-effect variability from which individual variability derives, including intrapatient, causing frequent fluctuations in their anticoagulant action. This makes the dose-response relation unpredictable for a given person and potentially unstable in the course of prolonged treatment. This variability leads to the intersection between the search for sufficient anticoagulation and the danger of hemorrhage. Strict control of anticoagulant therapy is necessary, above and beyond simply ensuring satisfactory analytical results. In itself, the interpretation of these findings requires a true medical intervention that involves care, prevention, aid, and recommendations to patients. However, physicians poised at this intersection particularly fear hemorrhage, especially in patients with a high INR (International Normalized Ratio), because the consequences of this complication are usually more somber than those of embolism. It is well known that an elevated intensity of anticoagulation is related to a greater risk of hemorrhage. Various authors have suggested that INR>5 is related with an increased risk of hemorrhage compared to patients with INR values within therapeutic range.1-3

Among the heart diseases that most frequently lead to beginning anticoagulant treatment is atrial fibrillation (AF). Various studies of non-rheumatic AF have been made to evaluate the reduction in thromboembolic events achieved with anticoagulant medication. In a meta-analysis of the first five studies (AFASAK, BAATAF, CAFA, SPAF-I and SPINAF),4 the annual rate of major hemorrhage in the control group did not differ significantly from that of the group with anticoagulation (1% vs 1.3%, respectively). Nevertheless, the incidence of severe hemorrhage in the meta-analysis has been criticized: the incidence in AFASAK I7 was surprisingly low when the established INR range was 2.8-4.2. The AFASAK II6 study by the same group found that an INR range of 2-3 was accompanied by an incidence of much more severe hemorrhage. In addition, the BAATAF7 and SPINAF8 studies were made with a therapeutic range of INR<2.

The relation between advanced age and a greater risk of hemorrhage seems reasonable, since this population has a greater number of concomitant diseases. This hypothesis is confirmed by the findings of the SPAF-II study,9 which assessed the incidence of hemorrhage in relation to age in patients with non-rheumatic AF treated with anticoagulants. It was observed that patients over 75 years had a significantly greater annual rate of major hemorrhage than patients under the age of 75 years (4.2% vs 1.7%, respectively).

Other studies have assessed the incidence of hemorrhage in outpatients treated with oral anticoagulants who had different diseases, cardiological or others. The ISCOAT study,10 which was a multicenter, prospective study that included 2745 patients, found an incidence of fatal hemorrhage of 0.25, major hemorrhage 1.1, and major/minor hemorrhage 7.6 percent patient/year. Nevertheless, there were difficulties in assessing the true incidence of hemorrhagic complications in different studies, emphasizing the following: methodological limitations, studies made before INR was introduced, some of which were retrospective and did not have a well defined cohort, and variations between therapeutic range in different studies.

Few studies have examined the identification of factors responsible for an excessively elevated INR value in patients with heart disease treated with anticoagulants, so controversy regarding this point still persists.11-13 Among these factors can be emphasized age, concomitant medication, alcoholism, recent onset of anticoagulant treatment, and variations in previous doses.

The objectives of the present study were a) to assess the incidence of excessive anticoagulation (INR>5) in patients with heart disease treated with acenocoumarol (Sintrom®) as outpatients; b) to compare the population of patients with excessive anticoagulation to a control group in order to identify the factors related to this overdose, and c) to observe the incidence and type of hemorrhage in poorly controlled patients.

PATIENTS AND METHOD

Patients

The study had a prospective observational design and a follow-up period of 7 months. It began in January 2000 and was finalized in July 2000. The population included patients with heart disease who being were treated on an outpatient basis with acenocoumarol anticoagulants at the time of study. The cardiology department of our center was
responsible for administering anticoagulant treatment to 512 patients with heart disease during the study period in a specific unit. The patients who had an INR within the therapeutic interval continued with the same regimen, and a new control was made one month later.

The study group, or the group of excessive anticoagulation, included 55 patients who had obtained at least one determination of INR>5 during the follow-up period. This value was considered the cutoff point because it has been reported in the literature that the risk of hemorrhage seems to increase from INR>5. The control group was formed by 49 patients who had an INR strictly within the therapeutic interval, according to the guidelines for clinical intervention of the Sociedad Española de Cardiología (Spanish Society of Cardiology) (INR=2-3) at the time of the study. The remaining patients, a total of 512, did not meet requirements for inclusion in one of the two groups.

A personal interview was conducted with all the patients included in the study on the day they were scheduled for a control visit, who underwent assessment of the clinical evolution in cases of anticoagulant overdose until test results were within the therapeutic range. The following data were collected: age, weight, sex, living alone, presence of someone who supervised medication, reason for anticoagulation, cardiac prosthesis, weekly dose, date of onset of anticoagulation, addition or discontinuation of a medication, and whether it interfered with Sintrom®, concomitant medication (number and type), current heart failure, alcohol use, liver disease, kidney failure, malnutrition, intercurrent disease or hospital admission in the month before the control, correct compliance (dose and schedule), and bleeding or embolism during follow-up.

Control of anticoagulation

Oral anticoagulation was monitored by prothrombin time, expressed as INR. The thromboplastins used in the laboratory had an ISI (International Sensitivity Index)<1.05. Patients went to the laboratory for INR determination, then received therapeutic guidelines for acenocoumarol treatment. If INR was within therapeutic range, the patients returned for control 30 days later. All the patients who underwent control of their anticoagulation in our center are given an information pamphlet with recommendations for patients who receive oral anticoagulants. These guidelines include a list of drugs that should not be used because they interfere with treatment with acenocoumarol and drugs that can be safely associated. A contact telephone for the unit is provided for patients who need to resolve doubts.

Patients (INR>5) with excessive anticoagulation were advised to discontinue acenocoumarol on the day the analysis was made. They were scheduled the next day for a new analysis. Oral or intravenous vitamin K administration was recommended depending on the IVR value or manifestations of bleeding. Periodic clinical controls and analyses were made until the therapeutic range was achieved.

Hemorrhagic complications

Hemorrhage was considered major if it required hospitalization or transfusion. Other bleeding episodes were categorized as minor. The type of hemorrhage that the patient presented was recorded.

Statistical analysis

Statistical analysis was carried out with the SPSSwin program. Quantitative variables were expressed as mean± standard deviation and qualitative variables as proportions (percentages). The comparison between two means was made with the Student t test and the comparison between proportions, by means of the $\chi^2$ test. A $P<.05$ value was considered statistically significant. Multivariate analysis was carried out by logistical regression analysis.

RESULTS

The total study population (104 patients) had a mean age of 70.8 years (range, 44-95 years) and the reasons that motivated the use of anticoagulant treatment were the following: atrial fibrillation or atrial flutter in 77% of the population (80 patients), left atrial dilation and AF in 70.2% (73 patients), mitral valve disease, associated to AF or not, in 66.5% (69 patients), heart failure or depressed ventricular function, associated or not to AF, in 46.1% (48 patients), arterial hypertension associated to AF in 39.4% (41 patients), mechanical valve prostheses in 34.6% (36 patients), and ischemic heart disease and AF in 21.1% (22 patients). Diabetes mellitus associated to AF, cerebrovascular accident, associated or not to AF, peripheral arterial embolism, associated or not to AF, pulmonary thromboembolism, and intracavitary thrombosis were less frequent motives for anticoagulant treatment (Figure 1). During the study period, 3683 INR determinations were made in 512 patients who underwent periodic controls at our center. Seventy-seven tests with INR>5 were identified, which are equivalent to 2% of all determinations and corresponded to 55 patients. Thirty-one percent of the population with excessive anticoagulation (17 patients) had more than one INR>5 during the study period (13 patients on two occasions, 3 patients on three occasions, and 1 patient four times had determinations higher than 5 during follow-up) (Figure 2).
The mean INR value in the over-anticoagulated group was 5.94 (range, 5.01-8.24). Most of these patients (36 patients, representing 65.5% of the study group) had INR values between 5 and 6 (Figure 3). Only 0.5% of the tests made in the course of follow-up had INR>6.

The clinical variables of each group are summarized in Table 1. There were no statistically significant differences between groups in the variables age, weekly dose of Sintrum® in mg, creatinine concentration (mg/dL), supervision of the prescribed dose by another person, discontinuation of a drug in the previous days, or alcohol use. The group of patients with excessive anticoagulant treatment was characterized by a greater proportion of women (67.3% vs 47%; P=.04), lower body weight (67.3 kg vs 74.6 kg; P=.01), greater number of prescribed drugs (5.2 vs 4.1; P=.04), more frequent addition of new drugs to treatment in the last month (47.2% vs 14.2%;
P<.001), more frequent addition of drugs interacting with acenocoumarol (14.5% vs 0%; P=.006), a greater number of patients who lived alone (23.6% vs 6.1%; P=.01), a greater percentage of patients with mechanical valve prostheses (38.1% vs 12.2%; P=.03), worse compliance with the prescribed dose of acenocoumarol (85% vs 100%; P=.006), more frequent intercurrent disease in the last month (49.1% vs 10.2%; P<.001), period in which a greater number of hospital admissions was recorded (20% vs 2%; P=.005). Multivariate analysis identified as independent predictive variables of over-anticoagulation, mechanical valve prostheses, poor compliance with the prescribed medication, the addition of new drugs that interfere with acenocoumarol, and intercurrent disease in the last month.

As was mentioned previously, 47.2% of the patients with excessive anticoagulation (26 patients) had a greater number of new drugs added to treatment in the month before the control. The pharmacological groups most commonly added were nonsteroid anti-inflammatory antibiotics. The other drugs added are listed in Figure 4.

Patients with INR>5 had a significantly greater incidence of all bleeding episodes than the control group (21.8% vs 4.08%; P=.008) throughout follow-up (7 months), which corresponds to an annual rate of all bleeding episodes in 37.6% of the patients in the group of patients with excessive anticoagulation. In our population, most of the bleeding was minor (Figure 5). Only one patient in the study group had major hemorrhage (lower gastrointestinal tract bleeding that required blood transfusion). No embolic process was recorded.

**DISCUSSION**

Few studies have tried to investigate the cause of overdosing in patients with anticoagulant treatment,11,12,16 and contradictory results have been obtained in some of them. Most of the published information refers to warfarin use, and there have been few studies with acenocoumarol.16-19 The ISCOAT study10 included 2745 patients who received anticoagulant treatment, principally warfarin (64% of the patients included) and the rest, acenocoumarol. The present study attempts to identify the factors that

---

**TABLA 1. Results**

<table>
<thead>
<tr>
<th></th>
<th>Control group (n=49)</th>
<th>Group IVR&gt;5 (n=55)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>70.3</td>
<td>71.2</td>
<td>NS</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>74.6</td>
<td>67.3</td>
<td>.01</td>
</tr>
<tr>
<td>Weekly dose, mg</td>
<td>14.7</td>
<td>14.2</td>
<td>NS</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.1</td>
<td>1.1</td>
<td>NS</td>
</tr>
<tr>
<td>Number of drugs</td>
<td>4.1</td>
<td>5.2</td>
<td>.04</td>
</tr>
<tr>
<td>Lives alone, % (patient)</td>
<td>6.1 (3)</td>
<td>23.6 (13)</td>
<td>.01</td>
</tr>
<tr>
<td>Supervision, % (patient)</td>
<td>28.5 (14)</td>
<td>30.9 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Addition of drug, % (patient)</td>
<td>14.2 (7)</td>
<td>47.2 (26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Addition of interfering drug, % (patient)</td>
<td>0 (0)</td>
<td>14.5 (8)</td>
<td>.006*</td>
</tr>
<tr>
<td>Drug discontinuation, % (patient)</td>
<td>4 (2)</td>
<td>12.7 (7)</td>
<td>NS</td>
</tr>
<tr>
<td>Women, % (patients)</td>
<td>47 (23)</td>
<td>67.3 (37)</td>
<td>.04</td>
</tr>
<tr>
<td>Prosthesis, % (patients)</td>
<td>12.2 (6)</td>
<td>38.1 (21)</td>
<td>.03</td>
</tr>
<tr>
<td>Recent admission, % (patients)</td>
<td>2 (1)</td>
<td>20 (11)</td>
<td>.005</td>
</tr>
<tr>
<td>Compliance, % (patients)</td>
<td>100 (49)</td>
<td>85.4 (47)</td>
<td>.006*</td>
</tr>
<tr>
<td>Alcohol use, % (patients)</td>
<td>12.2 (6)</td>
<td>5.4 (3)</td>
<td>NS</td>
</tr>
<tr>
<td>Intercurrent disease, % (patients)</td>
<td>10.2 (5)</td>
<td>49.1 (27)</td>
<td>&lt;.001*</td>
</tr>
</tbody>
</table>

*Significant variables in multivariate analysis.
caused excessive anticoagulation in patients treated with acenocoumarol. The studies cited in the literature on cohorts of patients treated with anticoagulants usually include patients with cardiac, vascular, or neurological diseases. Our series only included patients who received anticoagulants for cardiological reasons.

Factors predictive of elevated INR

Some authors have found a greater tendency toward hemorrhagic complications in older patients, whereas others do not consider age to be an independent risk factor. Our study found no age differences between the two groups. Other investigators have specifically found that the variability of the control of anticoagulation in older patients was not affected by social status, mobility, visual acuity, or at-home supervision of medication. In the present study, living alone or the existence of supervision were not independent risk factors for excessive anticoagulation, although the factor «living alone» was significant in univariate analysis.

The findings of the present study are comparable to those published in the literature with respect to pharmacological interactions as a risk factor for overdosing. The drugs most frequently added in the different studies were antibiotics. Likewise, we found that the medications most often added to treatment were antibiotics and nonsteroid anti-inflammatory drugs. As mentioned earlier, all patients received a guide with recommendations about treatment with oral anticoagulants, which listed medications that produce pharmacological interactions and medications that can be used safely.

In both study groups, a large number of concomitant drugs were administered, a mean of 5.2 drugs in the high INR group and 4.1 in the control group. This is not surprising, given the mean age of the population (70.8 years), which usually is associated with multiple pathologies and the use of various medications. There were no statistically significant differences between the two groups.

We and other authors have found that poor therapeutic compliance (incorrect dose or schedule) was a major instability factor in the outpatient control of patients treated with anticoagulants.

The presence of intercurrent disease in the previous month was a risk factor for overdosing. In the study by Bridgen et al., a possible cause of excessive anticoagulation was identified in 44 patients in the group of elevated INR (>6), 4 of which had a decompensated systemic disease.

One of the risk factors identified in the multivariate analysis was the presence of a mechanical valve prosthesis. The study by Bridgen et al. also showed that the group of patients with excessively high INR had artificial heart prostheses significantly more often. In our study, all the patients with mechanical cardiac prostheses had a range of anticoagulation with an INR of 2.5 to 3.5, whereas the recommended level of anticoagulation in patients who did not have prostheses was INR 2 to 3. Therefore, since prostheses carriers had a higher level of anticoagulation, we believe that the predictive factor for overdosing is the recommended INR interval and not having a mechanical valve prosthesis.

Level of over-anticoagulation

The INR level at which there is a greater risk of bleeding is debated. The ISCOAT study documented a greater incidence of bleeding when INR>4.5. Several studies have suggested that the risk of hemorrhage is inconsistent at INR<5. INR>5 seems to be accompanied by a small increment in the risk of hemorrhage with respect to the patients who are within therapeutic range. These were the reasons why INR>5 was established as the cutoff point for identify patients with excessive anticoagulation.

Most of these patients had INR between 5 and 6 (65% of patients). The overall incidence of overdosing was 2% of all the tests, and only 0.5% of tests made during follow-up were >6. These findings do not differ excessively from those of the study by Bridgen et al., which audited the frequency of excessive anticoagulation (INR>6) in a large number of tests (29 000), and found it to be 0.2%.
Incidence of bleeding

The overall incidence of all bleeding episodes (major and minor) in patients with INR>5 in our study was 21.8%, two times greater than the figure reported by Brigden et al. in patients with INR>6 (10.7%). We should keep in mind that this last study was a review, so it could have underestimated the frequency of minor hemorrhage. Personal interviews were conducted with patients when analyses were made of Sintröm. They were specifically interrogated about the presence of minor hemorrhage (nosebleed, bleeding gums, etc.). In our study we found an annual rate for all bleeding of 37.6% of the patients in the group of excessive anticoagulation (INR>5). In the ISCOAT study, when we analyzed the rate of hemorrhage in patients with INR between 4.5 and 7, we found bleeding in 40.5% of patients, which is an incidence similar to the one reported in our study.

Study limitations

One of the limitations of our work is the criterion for the inclusion of patients in the control group. Patients who had INR values strictly within the recommended therapeutic interval throughout the study and in the three months before inclusion were considered controls. Thus, patients who had recently begun treatment with oral anticoagulants were excluded. Consequently, one of the predictive factors of excessive anticoagulation described in the literature, the recent onset of treatment, could not be analyzed in our study.

Multiple variations in the dose of anticoagulants have been implicated as a significant risk for unstable control and associated hemorrhage. For the same reason mentioned in relation to the inclusion of patients in the control group, this factor could not be analyzed.

CONCLUSIONS

In our population of patients with heart disease treated with acenocoumarol on an outpatient basis, there was an acceptable rate of excessive anticoagulation, which did not differ from the rates reported in the literature.

Patients with INR>5 had a significantly greater incidence of total hemorrhage with respect to the control group, for the most part minor hemorrhage. Only one patient had major hemorrhage.

Special precautions must be taken when anticoagulant treatment is given to patients with mechanical prostheses and new drugs that interfere with acenocoumarol are added, intercurrent disease occurs in the last month, and it is suspected that compliance with the prescribed medication is incorrect.

REFERENCES

17. Meschengieser SS, Fondevila CG, Freixa R, et al. Comparison of two levels of anticoagulant