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Research Article

Inadequate Use of the Drug Acenocoumarol in Non-Valvular Atrial Fibrillation

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Abstract

No one can deny the great contribution that Acenocoumarol has made as an anticoagulant, mainly through its use in non-valvular atrial fibrillation.

However, there are currently other types of anticoagulants that do not require such exhaustive INR control and therefore have fewer side effects than Acenocoumarol.

Spain is one of the few countries in Europe that still prescribes Acenocoumarol, similar to warfarin. So much so that primary care physicians are not allowed to prescribe other anticoagulants that are more effective and less bothersome for the patient when taking the digital INR test. The study was performed in a primary care health system and secondary category hospitals. We were setting in a population of 2650 inhabitants in southeastern Spain (Number of patients to be treated is sufficient) with non-valvular atrial fibrillation and acenocoumarol takers. The follow-up time was 12 months.

The statistical study was limited to an "observational/descriptive" study, taking into account the variations and lability of the INR value (International Normalized Ratio), whose figures universally considered-regardless of the type of cardiovascular pathology-have been proposed to be between 2 - 3, in a maximum term of one determination every 28 days, regardless of the figures obtained concerning previous ones.

Given that the vast majority of Acenocoumarol intake occurs in elderly patients-over 65 years of age-and that these individuals are usually subject to a polymedication regimen, the medications taken by each of them were a fundamental reason for the assessment.

As fundamental conclusions in this clinical study, we must say that: In time between INR determination and last intake of food and medication are not being correct; they tend to be anarchic INR determinations and when it is most convenient; research regarding drugs taken concomitantly with Acenocoumarol practically does not exist.

Keywords: *Anticoagulants; Acenocoumarol; Misuse of Anticoagulants; Non-Valvular Atrial Fibrillation*

Introduction

No one can deny the great contribution that acenocoumarol has made as an anticoagulant, mainly through its use in non-valvular atrial fibrillation [1].

However, there are currently other types of anticoagulants that do not require such exhaustive INR control and therefore have fewer side effects than acenocoumarol [2-6].

These kind of anticoagulants are potent, reversible, direct and highly selective oral factor Xa inhibitors. It does not require antithrombin III for antithrombotic activity. It inhibits free and clot-bound factor Xa and prothrombinase activity. It has no direct effect on platelet aggregation, but indirectly inhibits thrombin-induced platelet aggregation. By inhibiting factor Xa, a drug as apixaban - for example - prevents both thrombin generation and thrombus formation.

Preclinical studies with apixaban in animal models have demonstrated antithrombotic efficacy in the prevention of arterial and venous thrombosis at doses that preserve hemostasis. They're preferably used for the treatment of prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (NVAF) with one or more risk factors such as previous stroke or transient ischemic attack (TIA); age ≥ 75 years; hypertension; diabetes mellitus; symptomatic heart failure (≥ NYHA class 2). Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adult patients.

Acenocoumarol is the most commonly used anticoagulant in the indicated places (southeastern Spain). Especially in people over 65 years of age, regardless of sex [7,8].

The pathology where it is most prescribed is atrial fibrillation of non-valvular origin, and these people were the target of the study.

The INR (International Normal Range) lability was assessed and cross-checked concerning individual medication, feeding types, and concomitant medication with Acenocoumarol. And, above all, at the time of determination of the INR range in each person (during the time -in hours- elapsed from the last nocturnal food intake to the time of the morning INR test and regular proton pump inhibitor takers (mainly Omeprazole).

Pharmacology [2]

Action and mechanism: Anticoagulant with coumarin structure. It acts by inhibiting the action of vitamin K on the gamma-carboxylation of specific glutamic acid molecules located in coagulation factors II (prothrombin), VII, IX, X, and anticoagulant proteins C and S and without which blood coagulation cannot be triggered. The anticoagulant effect is maximal after one or two days and lasts for two days after discontinuation of treatment. Compared to warfarin, it has a shorter duration, which is an advantage in case of hemorrhage. In contrast, inconclusive data suggest that once-daily doses have more significant fluctuations in anticoagulant effect throughout the day than warfarin, with a higher risk of bleeding during prolonged treatment.

Pharmacokinetics:

- **Orally:** Absorption is rapidly absorbed through the gastrointestinal tract (T max = 3 - 4h) with systemic bioavailability of at least 60%. The AUC of plasma concentrations is proportional to the administered dose in 8 - 16 mg. The beginning of the action is 24 - 48 hours. Coagulation factors return to pre-treatment values two days after treatment suspension.
- **Distribution**: The precise time for the action to appear is 2 hours, and its duration is 48 hours. Acenocoumarol passes into breast milk in virtually undetectable amounts and crosses the placental barrier. The degree of binding to plasma proteins is 99%. Metabolization is extensively metabolized in the liver by CYP450, isoenzyme CYP2C9. A genetic polymorphism for this isoenzyme has been identified. It has at least one metabolite with significant biological activity.
- **Elimination**: The half-life of Acenocoumarol is discreetly short, between 10 and 24 hours (this is why the importance of the INR value obtained from the last nocturnal intake and the performance of the digital puncture to obtain the INR value). The 30% is eliminated with urine in metabolized form and < 1% in unchanged form. The cumulative excretion of metabolites and unchanged active substance over eight days is 60% of the dose in the urine and 29% of the dose in the feces.

Of the 2650 patients undergoing anticoagulation therapy with Acenocoumarol, about 60% showed a high degree of lability in INR values. With supposedly incomprehensible rises and falls with respect to the ranges 2 - 3.

Interactions: Oral anticoagulants are drugs that can give rise to many interactions, among which those of clinical relevance will be described (Table 1). Acenocoumarol particularly has high interaction with some drugs commonly used by people in this age range, namely Omeprazole and Statins (Very rigorous studies on the possible interactions between the different lipid-lowering agents and acenocoumarol indicate that the least harmful is Atorvastatin).

The most important mechanisms related to these interactions are absorption disorders, inhibition or induction of the metabolizing enzyme system, displacement of plasma protein binding, and reduced vitamin K availability. Strict coagulation control is required when a drug is administered in combination with a coumarin anticoagulant or discontinued their concomitant administration. Most of the interactions are documented in a small number of cases or isolated cases. Most studies have been carried out with warfarin and not with Acenocoumarol, so it is often assumed that the interaction affects both anticoagulants equally.

- **Enzyme inducers**: There are studies in which inhibition of the anticoagulant effect has been recorded due to induction of its hepatic metabolism when administered together with: aminoglutethimide, griseofulvin, rifampicin.
- **Enzyme inhibitors**: There are studies in which potentiation of the anticoagulant effect has been recorded, with risk of bleeding, due to an inhibition of their hepatic metabolism when co-administered with: antiarrhythmics (amiodarone), antibacterials (ciprofloxacin, clarithromycin, erythromycin, roxithromycin, pefloxacin, chloramphenicol), capecitabine, cyclosporine, cimetidine, fluconazole, tamoxifen, viloxazine.
- Drugs that displace anticoagulants from their binding to plasma proteins, with potentiation of anticoagulant activity: nalidixic acid, non-steroidal anti-inflammatory drugs (phenylbutazone, flurbiprofen, piroxicam), benziodarone, carnitine, miconazole. There are some studies with chlorpropamide. An increase in the half-life of the antidiabetic has been recorded, with possible potentiation of its effect, due to displacement of its binding to plasma proteins.
- Decreased availability of vitamin K, with consequent potentiation of anticoagulant activity: thyroid hormones (levothyroxine, liothyronine), penicillins.
- Drugs that decrease the synthesis of coagulation factors, with consequent potentiation of the anticoagulant effect: danazol, paracetamol (especially at high doses, so it is considered a therapeutic alternative to salicylates), quinidine, quinine, vitamin E (tocopherol).
Other mechanisms:
- **Acarbose**: There is a study with warfarin in which possible potentiation of the anticoagulant effect has been recorded. The mechanism has not been established.
- **Anticancer drugs** (azathioprine, mercaptopurine): Some studies with warfarin have reported a decrease in the anticoagulant effect due to possible antagonism of their effects.
- **Oral contraceptives:** There are studies in which a decrease in the anticoagulant effect has been recorded, although this effect has been potentiated in others. This seems to be due to the balance between different effects of the estrogenic component of contraceptives, which may predominate its procoagulant effect through an increase in the synthesis of coagulation factors, or its anticoagulant effect through inhibition of the hepatic metabolism of the anticoagulant.
- **Corticosteroids:** The administration of corticosteroids at high doses could increase or decrease the effects of oral anticoagulants. However, there are no data to establish the effects of corticosteroids at low or moderate doses on INR. Therefore, it is recommended to monitor the response to the anticoagulant.

- **STATINS:** A case of potentiation of the anticoagulant effect with simvastatin has been described. In addition, Lovastatin, fluvastatin, and atorvastatin (very slightly) potentiate the effects of warfarin. Therefore, caution is recommended, monitoring the INR when initiating or suspending treatment with statins and when changing their dosage.
- **Fusidic acid:** Possible increase in anticoagulant activity. The mechanism of this possible interaction is not known at this time.
- **Raloxifene**: Some studies have reported a possible decrease in prothrombin time. The mechanism has not been established.
- **Salicylates (acetylsalicylic acid, diflunisal):** There are studies in which a possible potentiation of the anticoagulant effect has been reported, with risk of hemorrhage.
- **Tetracyclines (doxycycline):** Some studies have reported potentiation of the anticoagulant effect, with risk of bleeding, due to the addition of their hypothrombinemic effects.
Among all the interactions with other drugs (severe, moderate, and mild), the present study paid particular attention to interactions with Omeprazole and hypolipidemic agents (including fibrates).
These drugs were being taken by almost 100% of people to palliate different concomitant pathologies.
Omeprazole
The interaction has been studied in clinical practice, describing increases in prothrombin time and INR and several cases of potentiation of the hypoprothrombinemic effect of the anticoagulant. Although there are contradictory data in which no such effect has been reported, the interaction seems possible. Possibly, the best option is to substitute omeprazole for another anti-ulcer drug. If this is impossible, both INR and prothrombin time should be monitored when omeprazole is added or discontinued during concomitant treatment with anticoagulants. In some cases, it may be necessary to consider a reduction in the dose of the anticoagulant.
Effect: Possible reduction in the elimination of the anticoagulant, with the consequent risk of hemorrhage. **Importance**: The interaction has been studied in clinical practice, describing increases in prothrombin time and INR and several cases of potentiation of the hypoprothrombinemic effect of the anticoagulant. Although there are contradictory data in which no such effect has been reported, the interaction appears to be possible. Possibly, the best option is to substitute omeprazole for another anti-ulcer drug. If this is impossible, both INR and prothrombin time should be monitored when omeprazole is added or discontinued during concomitant treatment with anticoagulants. In some cases, it may be necessary to consider a reduction in the dose of the anticoagulant. **Mechanism:** Possible inhibition of hepatic metabolism of the anticoagulant by omeprazole. This drug seems to affect the hepatic metabolism of the R-isomer of warfarin (R-warfarin), which is 3-6 times less active as an anticoagulant than S-warfarin. **Evidence:** 1. In a double-blind, crossover study on 21 healthy volunteers, administration of omeprazole (20 mg/day) with warfarin (in individualized doses) for two weeks caused a slight increase in the blood levels of (R)-warfarin without affecting those of (S)-warfarin. In addition, a slight increase in hypoprothrombinemic activity, measured in terms of Thrombotest, was observed. 2. Ahmad describes the appearance of bruising and hematuria, with a prothrombin time of 48 seconds (four times higher than average) in a man stabilized on warfarin (5 mg/day) after two weeks of treatment with omeprazole (20 mg/day). After discontinuation of warfarin administration, it took five days for prothrombin time to normalize. After this, warfarin therapy was reinstated at a 2 mg/day dose, maintaining the prothrombin time within physiological limits. A clinical case is a 78-year-old female patient who was stabilized on Acenocoumarol and who developed hematuria after initiating treatment with omeprazole (20 mg/d). Her INR increased from 2.5/3 to 5.7 and decreased again when omeprazole was withdrawn.

Table 1: *Main drugs influencing acenocoumarol pharmacology.*

Methods

The statistical method was descriptive-observational. The variables assessed were INR lability, Omeprazole intake, Lipid-lowering agents, and the relationship between the last food intake and the determination of the INR value.

All the patients assessed had been diagnosed with non-valvular atrial fibrillation and were taking acenocoumarol.

Universe assessed: 2650 people had manifest lability of the INR value (we consider INR lability when the difference in values obtained in five INR determinations is more significant than 78%, for five consecutive weekly determinations, with values higher or lower than the basal values).

The drugs evaluated concerning INR lability were mainly:

- Omeprazole
- Statins.

Finger prick determinations of INR values were performed in all patients assessed weekly until we were sure that no or acceptable INR lability (less than 30% of average values: 2 - 3) had been reached.

Exclusion criteria

Any patients who have coagulation alterations unrelated to non-valvular atrial fibrillation (At the beginning of the essay, patients with INR lability were 100%).

Results and Discussion

100% of all patients had atrial fibrillation of non-valvular origin and lability in INR figures obtained by finger prick.

According to the obtained INR, the next finger puncture was between 2 and 7 days.

The total follow-up time was 12 months.

Once the disappearance of INR lability was achieved, finger punctures were every 28 days.

Before the clinical trial finished, the number of patients in whom INR lability disappeared for more than three months was 53 (97.95%) (Table 2).

Conclusion

Conclusions about essay

In primary care centers and hospitals of secondary care, according to the data obtained on the universe assessed, we can conclude the following points to achieve better INR values and avoid lability as much as possible:

1. Always take into account the half-life of Acenocoumarol and avoid less than 12 hours between the INR determination and the patient's last intake. Taking into account the half-life of acenocoumarol-8 to 12 hours -any new drug intake in a time shorter than these numbers would increase the amount of the drug in the patient's bloodstream. Therefore, the INR figures would be higher than those expected if the new intake ranged between 10 and 12 hours.
2. The intake of Omeprazole and derivatives shall be exhaustively evaluated. If there is a manifest INR lability, the most appropriate is to replace the "proton pump inhibitor" with other antacids of the histamine two antagonist type".

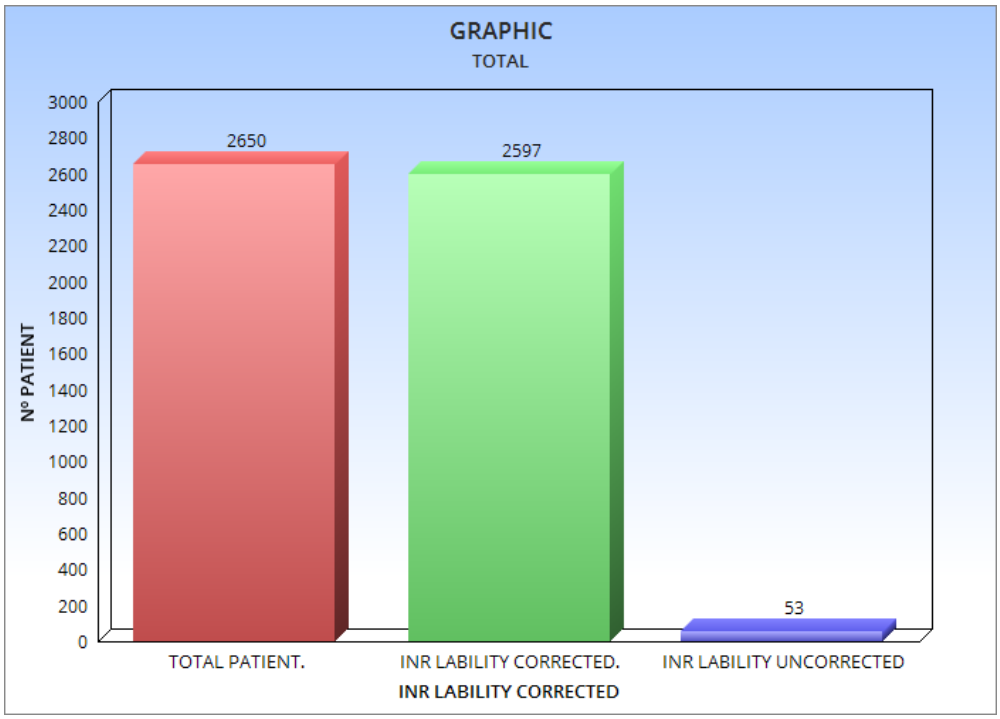

Table 2

Conclusions from the author [1]

Although it is true that the price of acenocoumarol is much lower than that of the new generation anticoagulants, this should not be an obstacle in so-called first world countries, such as Spain in this case.

INR evaluators should always keep in mind that to obtain the most reliable value:

- The timing of the finger stick should be in relation to the patient's last food intake. On average, ten hours should have elapsed since the last intake of food.
- They should also consider whether the patient is a regular user of proton pump inhibitors.
- In Spain, these two necessary conditions are not usually taken into account.
- The inconvenience for the elderly to undergo digital puncture for INR calculation would be practically non-existent.

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