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Analysis of acenocoumarol and levofloxacin interaction in elderly institutionalized patients

Análisis de la interacción de acenocumarol y levofloxacino en ancianos institucionalizados

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Abstract

Objective: To analyze the interaction between acenocoumarol and levofloxacin in the elderly. We also assessed how hypoalbuminemia affects international normalized ratio variation.

Method: Retrospective study carried on elderly institutionalized patients who were prescribed levofloxacin concomitantly with acenocoumarol. International normalized ratio variation during levofloxacin treatment was analyzed with the t-Student test. Correlation between albuminemia and international normalized ratio variation was calculated using Pearson's correlation coefficient.

Results: The mean international normalized ratio previous to treatment with levofloxacin was 2.5 (standard deviation: 0.6) and during treatment it was 4.7 (standard deviation: 1.9) ($p < 0.05$). In 54.3% of the cases, the international normalized ratio value was equal to or greater than 4.5. Not linear association between albuminemia and international normalized ratio increase was found using Pearson's test ($R = -0.16$).

Conclusions: In more than half of the occasions international normalized ratio raised to clinically rellevant values (≥ 4.5). No influence of hypoalbuminemia in the increase in international normalized ratio was shown.

Resumen

Objetivo: Analizar la interacción levofloxacino-acenocumarol en ancianos y determinar la influencia de la hipoalbuminemia en el incremento del *international normalized ratio*.

Método: Estudio observacional retrospectivo en ancianos institucionalizados que recibieron simultáneamente acenocumarol y levofloxacino. Se analizó la variación del *international normalized ratio* durante el tratamiento con levofloxacino mediante la prueba t-Student. Se estudió la relación entre la albuminemia y la variación de *international normalized ratio* mediante el coeficiente de correlación de Pearson.

Resultados: La media de *international normalized ratio* previa al tratamiento con levofloxacino fue de 2,5 (desviación estándar 0,6) y durante el tratamiento fue de 4,7 (desviación estándar 1,9) ($p < 0,05$). En el 54,3% de los casos el valor de *international normalized ratio* fue igual o superior a 4,5. La prueba de Pearson no mostró asociación lineal entre la albuminemia y el incremento de *international normalized ratio* ($R = -0,16$).

Conclusiones: En más de la mitad de las ocasiones, el *international normalized ratio* alcanzó valores de relevancia clínica ($\geq 4,5$). No se evidenció influencia de la hipoalbuminemia en el incremento del *international normalized ratio*.

Introduction

Acenocoumarol is an oral anticoagulant that inhibits the action of vitamin K present in coagulation factors II, VII, IX, and X[1]. This mechanism of action is the same as that of warfarin. Both anticoagulants are indicated for the prevention and treatment of thromboembolic disorders. These anticoagulants have high intra- and interindividual variability due to environmental and genetic factors (e.g. age, sex, weight, diet, substance use, genetic polymorphisms)[2] and narrow therapeutic indexes. In addition, they interact with many drugs due to their pharmacokinetic characteristics, such as binding to plasma proteins and hepatic metabolisation through cytochromes CYP2C9, CYP2C19, or CYP1A2[1].

The effect of vitamin K antagonists (VKA) was assessed by determining the prothrombin time, which was expressed as the international normalized ratio (INR). It has been found that in patients treated with VKA the incidence of bleeding exponentially increases for INR values greater than 4.5[3].

Most drug interaction studies have been conducted using warfarin, and the results have been extrapolated to acenocoumarol. Published studies that have analysed their interaction with fluoroquinolones have found an increase in their anticoagulant effect. For certain quinolones, it has been suggested that the mechanism of action of this interaction is displacement from their binding sites to plasma proteins[4,5]. Some studies have addressed interactions with levofloxacin, which is a widely prescribed antibiotic. However, such studies are scarce and most of them are short case series[6-8].

Elderly patients often have comorbidity and polypharmacy, which are risk factors for drug interactions. In addition, age itself is considered to be a risk factor for bleeding during VKA treatment[9]. Furthermore, albumin levels are generally lower in the elderly population[10]. Therefore, the study of acenocoumarol interactions in this population is of interest.

The main objective of this study was to analyse levofloxacin-acenocoumarol interactions in institutionalized elderly patients. The secondary objective was to assess the role of hypoalbuminemia in increased INR values.

Methods

A retrospective observational study (October 2011-January 2016) of institutionalized elderly patients in nursing homes for dependent elderly individuals included in a coordinated oral anticoagulant treatment follow-up program conducted by a Pharmacy Service. Cases were included in which the patients had received concomitant acenocoumarol and levofloxacin. We excluded cases in which the INR value was not available during levofloxacin treatment. The following variables were obtained from the medical records: demographic variables (sex, age), number of drugs, relevant disease, indications for anticoagulant treatment, and analytical values of serum creatinine and albumin. In the descriptive analysis of these data, continuous quantitative variables are expressed as median and range, and categorical variables are expressed as relative frequency (percentage). Pharmacotherapeutic histories were reviewed to identify treatments that could interact with acenocoumarol.

In each case of the concomitant administration of levofloxacin-acenocoumarol, the INR values were measured before and during antibiotic treatment. The two ranges were compared using the Student *t* test for

Tabla 1. Demographic variables, concomitant medication, and relevant disease.

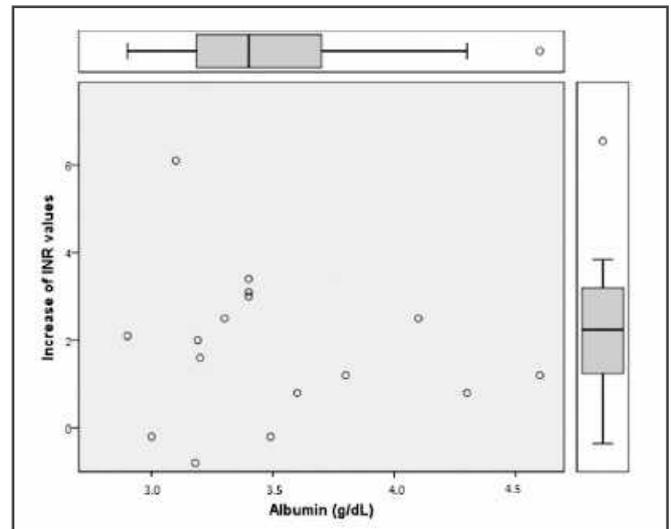| Variable	
Sex	58.3% men 41.7% women
Age, years (median [range])	82 (57-92)
Number of drugs (median [range])	9 (4-17)
Heart failure	63.6%
Hypertension	63.6%
Previous thrombotic events	40.9%
Chronic obstructive pulmonary disease	27.3%
Ischemic heart disease	27.3%
Dyslipidaemia	22.7%

Figure 1. *Pearson correlation test of albumin values and increased INR during levofloxacin treatment.*

related samples. An INR value ≥ 4.5 was used as a cutoff for statistical significance. The drug interaction probability scale (DIPS)[11] algorithm was applied in each case of interaction (score: > 8 highly probable, 5-8 probable, 2-4 possible, < 2 doubtful). We also recorded if vitamin K administration was needed, and calculated changes to the weekly dose of acenocoumarol.

The relationship between the patients' albumin levels and variations in the INR was analysed using the Pearson correlation coefficient, applying a one-tailed test of statistical significance.

All data were analysed using the SPSS® version 23.0 software package.

Results

We identified 48 cases of the concomitant administration of levofloxacin-acenocoumarol in 27 patients. Thirteen cases were excluded because the INR value was not determined during levofloxacin administration. The final sample comprised included 24 patients (35 cases).

Table 1 shows the demographic variables, relevant diseases, and concomitant medication (treatment for chronic disease at the time of interaction). Indications for anticoagulant treatment were atrial fibrillation and deep vein thrombosis in 88.9% and 11.1% of the patients, respectively. Regarding renal function, serum creatinine values were available in 24 cases (mean: 0.9 mg/dL, standard deviation [SD]: 0.4). The creatinine value exceeded 1.2 mg/dL in just three cases. According to the information contained in the pharmacological histories, three additional medications were identified that could potentially interact with acenocoumarol (amiodarone, levothyroxine, and megestrol acetate). However, no changes were made to the dosage of these drugs during levofloxacin treatment.

The mean INRs before and during levofloxacin treatment were 2.5 (SD: 0.6) and 4.7 (SD: 1.9), respectively. This difference was statistically significant (*P* < 0.05). During antibiotic treatment, the INR values were equal to or more than 4.5 in 54.3% of cases, more than 3 and less than 4.5 in 31.4% of cases, and equal to or less than 3 in 14.3% of cases. Application of the DIPS scale yielded a score of 5, which indicates that the interaction was "probable".

In five cases vitamin K was administered to reverse the anticoagulant effect. This was done in four cases because the INR was more than 8 and in one case because of haematuria with an INR equal to 6. No patient experienced major bleeding. The acenocoumarol dose was reduced during levofloxacin treatment in 29 of the 30 cases in which the INR was more than 3. In cases in which the INR was more than or equal to 4.5, the median percentage reduction of the dose was 25.5% (range: 0.0-16.7), and in cases in which it was more than 3 but less than 4.5 the reduction was 10% (range: 9.3-57.2).

In 16 cases, the mean albumin level was 3.49 g/dL (SD: 0.48). In the 14 patients with an INR equal to or more than 4.5, 7 albumin values were recorded, six of which were below 3.5 g/dL. No linear correlation was found between albuminemia and increased INR during levofloxacin treatment ($R = -0.16$) (Figure 1).

Discussion

A statistically significant increase in INR values was found during levofloxacin administration. Although a literature search found no other studies on institutionalised patients, the results are consistent with those found in a study on warfarin-levofloxacin interaction in a group of 30 hospitalized patients. The study found significant differences ($P = 0.001$) between the median of the INR before treatment with levofloxacin (1.85, 1.01-4.08) and the median during (2.64; 1.00-6.32) treatment[12]. The present study also found that when the patients received concomitant levofloxacin and acenocoumarol, the INR increased to clinically relevant levels (≥ 4.5) in more than half of the cases.

A review of the pharmacological treatments ruled out the possibility that the other treatments could have been changed such that they could have interacted with acenocoumarol during antibiotic treatment; thus, in the study patients, levofloxacin appears to have had a relevant role in this interaction.

The present study was conducted in institutionalized patients in whom specific factors that could affect coagulation (e.g. substance use) were controlled. Changes in diet were minimal. There were insufficient data to be able to assess the influence of kidney failure on changes in coagulation.

Although some studies conducted in patients anticoagulated with warfarin show that the probability of reaching an INR value above the therapeutic target is higher in patients with hypoalbuminemia[13,14], the results of the present study do not support an association between hypoalbuminemia and increased INR values. However, our data are limited and new studies would be needed to assess the role of hypoalbuminemia in this interaction.

In our setting, levofloxacin is a widely used antibiotic and the concomitant administration of acenocoumarol is common. Regarding the management of this interaction, although there is no need to avoid the concomitant use of quinolones and VKA anticoagulants[4], it is advisable to monitor the anticoagulant effect with greater frequency. Given that elderly patients are more sensitive to anticoagulant therapy, further studies of this type are needed to establish recommendations on the management of this interaction. Such recommendations should include guidelines on coagulation monitoring and proposals for reducing the anticoagulant before the administration of the antibiotic in patients at higher risk of adverse events.

Funding

Conflict of interests

No conflict of interests.

Contribution to the scientific literature

Elderly patients are very sensitive to anticoagulant therapy, and thus it is of interest to study levofloxacin-acenocoumarol interactions in this population. This study provides new data on the characteristics of this interaction in the elderly population and on the role of hypoalbuminemia in this interaction.

The results show that in a high proportion of cases the interaction was associated with an increase in INR values to clinically relevant levels. Therefore, recommendations are needed on the management of this interaction in elderly patients treated with acenocoumarol. Further studies are needed on hypoalbuminemia as a potential risk factor for adverse effects of the anticoagulant when both drugs are concomitantly administered.

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