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Case Report

A Mysterious Resistance to Acenocoumarol!

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Abstract

Acenocoumarol is the most widely prescribed vitamin K antagonist (VKA) to prevent and treat thromboembolic disorders. It keeps a major place in many indications despite the introduction of new direct oral anticoagulants (DOACs). However, a narrow therapeutic range, an intra-individual variability and drug interactions may lead to serious adverse drug reactions. Sometimes, a genetic or acquired resistance to this drug may lead to a risky situation. Hopefully, resistance to acenocoumarol is a very rare phenomen.

Here in we present an unsusual case of a suspected resistance to acenocoumarol. This case was notified to the Tunisian National Center of Pharmacovigilance on October 2017 and registered under the number 2449/2017.

A 67-year-old patient with hypertension, diabetes, and coronary disease was treated with captopril, atenolol, atorvastatin, and salicylic acid. In 2017, acenocoumarol treatment was introduced. At biological control, the prothrombin time (PT) was 100%. The doses of acenocoumarol were raised progressively with iterative controls of PT. PT was always 100% even when acenocoumarol reached the dose of 2 g/day. A resistance to acenocoumarol was suspected. The patient was referred to pharmacovigilance department for case analysis. During the patient interview, we discover that the patient was confusing acenocoumarol with atenolol. In fact, when his doctor was increasing the doses of acenocoumarol, the patient increased her intake of atenolol believing that it was acenocoumarol.

A resistance to acenocoumarol was eliminated in this patient since she had never taken the drug. We highlight through this case the importance of patient's interview. Explaining the indications and the potential adverse events of the drug to patients taking VKA is crucial to ensure a better efficiency of treatment without increasing the risk of bleeding complication.

Keywords: Vitamin K Antagonist; Anticoagulant; Acenocoumarol; Resistance; Pharmacovigilance

Abbreviations

VKA: Vitamin K Antagonist; DOACs: Direct Oral Anticoagulants; PT: Prothrombin Time; INR: International Normalized Ratio

Introduction

Acenocoumarol is the most widely prescribed vitamin K antagonist (VKA) to prevent and treat thromboembolic disorders. It keeps a major place in many indications despite the introduction of new direct oral anticoagulants (DOACs). However, a narrow therapeutic range, an intra-individual variability and drug interactions may lead to serious adverse drug reactions. Sometimes, a genetic or acquired resistance to this drug may lead to a risky situation. Hopefully, resistance to acenocoumarol is a very rare phenomen.

Materials and Methods

Here in we present an unsusual case of a suspected resistance to acenocoumarol. This case was notified to the Tunisian Center of Pharmacovigilance on October 2017 and registered under the number 2449/2017. It was analyzed according to the French updated method for the causality assessment of adverse drug reactions [1].

Results and Discussion

A 67-year-old patient with hypertension, diabetes, and coronary disease was treated with captopril, atenolol, atorvastatin, and salicylic acid. In 2017, acenocoumarol treatment was introduced. At biological control, the prothrombin time (PT) was 100%. The doses of acenocoumarol were raised progressively with iterative controls of PT. PT was always 100% even when acenocoumarol reached the dose of 2 g/day. A resistance to acenocoumarol was suspected. The patient was referred to pharmacovigilance department for case analysis. During the patient interview, it was found that the patient was confusing acenocoumarol with atenolol. In fact, when his doctor was increasing the doses of acenocoumarol, the patient increased his intake of atenolol believing that it was acenocoumarol. The patient had never taken acenocoumarol.

The responsibility of acenocoumarol was evaluated as I0 (C0) according to the updated French method of imputability because of the incompatible delay (the patient has never taken the drug) [1,2].

The prescription of acenocoumarol must be monitored by the "International Normalized Ratio" (INR) to adjust the posology, achieve the desired levels of anticoagulation capable of preventing thromboembolic events without increasing the risk of bleeding complications. The management of these complications remains a major challenge regarding their potential severity. In fact, an INR below 1.7 has been associated with a doubling of stroke risk, whereas an INR above 3.0 doubles the risk of major hemorrhage [3].

Despite a well-defined target range of INR for various indications and close monitoring of patients, large fluctuations in anticoagulant control are frequently noticed. In this regard, poor patient's adherence is the first cause of a floating INR. A good INR monitoring can be obtained via patients' behavior control. For example, patients with better knowledge and higher medication adherence are more likely to have good INR control [4]. Otherwise, the requirement of acenocoumarol's therapy is particularly frequent in older patients. In a prospective collaborative study, Palareti et al found that 30% of patients starting an anticoagulant treatment were 70 years and older [5]. The lack of knowledge about treatment in population of elderly subjects can severely affect patients' INR control. Actually, multiple comorbidities, polypharmacy, history of hypertension, insufficient social support, decreased access to care and reduced functional status are to blame [3,6]. Furthermore, cognitive impairment is thought by many physicians to be a contraindication for anticoagulant treatment [6].

Consistent with a previous Tunisian study, a moderate negative correlation was found between patients' knowledge of VKA therapy and age [7]. Elderly patients and patients with lower education were more likely to have poor knowledge of the treatment. Most of this study's patients were unable to indicate the consequences that may occur if VKA dosing is insufficient or if they do not take their medication. Only one-third of the study patients were aware of the importance of VKA therapy monitoring and one-fifth knew how VKA treatment should be monitored. This lack of knowledge may be due to the fact that over one-third of the patients were illiterate [7]. Yet, other investigators reported similar findings among patients with a higher level of education [4]. These results suggested that these patients may require special consideration. Innovative and patient-targeted educational programs and improvement of the physician-patient communication are needed regardless of education level. That kind of attitude may improve patients' knowledge, drug compliance, and adherence to medical advice.

In our case, thanks to a meticulous interview, we discovered that this 67-year old patient was confusing acenocoumarol with atenolol. This emphasize that a premature diagnosis of resistance should be avoided. Actually, true resistance to acenocoumarol, which is genetic, is extremely rare [8]. It is attributed to the presence of enzymes or receptor sites with altered affinity for vitamin K or the drug [9]. This sort of resistance is constantly primary and its diagnosis is complex because a highly detailed genetic study must be conducted. Absence of drug intake, a high vitamin K intake, drug interaction, malabsorption or increased destruction/metabolism of the drug may be sometimes mistakenly considered as a resistance situation.

Conclusion

A resistance to acenocoumarol was eliminated in this patient since she had never taken the drug. We highlight through this case the importance of patient's interview. Thus, a proper communication between patients and healthcare providers is essential. Explaining the indications and the potential adverse events of the drug to patients taking VKA is crucial to ensure a better efficiency of treatment without increasing the risk of bleeding complication.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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