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Study of the Clinical Impact of Drugs Interactions of Acenocoumarol

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Abstract

One of the problems linked to the use of acenocoumarol in therapy is the intra and interindividual variability of the doses necessary to obtain the desired INR; this may be due to several factors, including drug interactions. This is how we felt the need and the importance of undertaking this work which aims to identify the drugs most likely to interact with acenocoumarol and to assess the risk level of these interactions.

This is a prospective, single-center cross-sectional study from January 01, 2017 until April 30, 2017, conducted at the pharmacovigilance service of the Oran EHU. In order to assess the risk level of an interaction, we used an interaction weighting method which allowed us to calculate the criticality indices (CI).

The results highlighted 22 drugs at high risk of interacting with acenocoumarol of which amiodarone, omeprazole and diclofenac sodium are the most involved. This work was carried out with the aim of optimizing and securing acenocoumarol treatment.

Keywords: Acenocoumarol; drug interactions; criticality index.

1. Introduction

In Algeria, acenocoumarol is the only anti-vitamin K (AVK) available. One of the problems associated with the use of this anticoagulant is the existence of a great intra- and inter-individual variability of the doses necessary to obtain the desired International Normalized Ratio (INR). Such variability in drug response depends on several factors, including drug interactions (AMIs). Since warfarin is the most commonly prescribed VKA worldwide, most VKA drug interactions found in the drug literature concerns this coumarin derivative.

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However, the pharmacokinetics in particular the metabolism of warfarin is different from that of acenocoumarol, therefore these differences have a direct impact on drug interactions, especially those of a pharmacokinetic nature. The objective of this work is to analyze the drug prescriptions of our study population in order to target the drugs most at risk of interacting with acenocoumarol followed by a weighting of the level of risk of the interaction in s " based on the pharmacological data (kinetics and dynamics) of drugs co-prescribed with acenocoumarol.

2. Material and methods

2.1. Type and location of the study

This is a single-center cross-sectional prospective study running from January 01, 2017 to April 30, 2017, conducted at the level of the pharmacovigilance service of the EHU of Oran.

2.2. Study population

We included in our study patients treated with acenocoumarol for the following pathologies: embologenic heart disease (atrial fibrillation, mitral valve disease, valve prostheses, etc.), deep vein thrombosis, and benefiting from regular monitoring of the INR, some or their age, sex and associated treatments.

Excluded from our study, patients with a history of smoking, alcoholism, patients with a diet rich in vitamin K and patients with poor compliance.

2.3. Compendium of Acenocoumarol Drug Interactions

To establish the database of drug interactions of acenocoumarol, we gathered all the bibliographic data concerning drugs interacting with VKA using the following repositories and drug interaction detection software: VIDAL expert 2016 [1], Review Prescribe 2016 [2], Thesaurus of drug interactions ANSM 2016 [3], Slockley's Drugs Interactions 2014 [4]. These data were used to develop the guide to drug interactions of antivitamins K.

2.4. Collection of patient medication prescriptions


Service de Pharmacovigilance
Pr H.TOUMI

Fiche De Suivi Des Patients Sous Acénocoumarol

Nom : Prénom :

Né le: Poids : taille :

Pathologie traitée :

INR cible : ☐ [2-3], ☐ [2,5-3,5], ☐ [3 – 4],☐ autre :[-]

Paramètres demandés : ☐ TP ☐ TCK ☐ FIB ☐ INR

☐ Gène VKORC1 ☐ Gène CYP2C9

Date du début du traitement AVK :

Posologie initiale : INR de base :

Posologie actuelle de l'Acénocoumarol : cp/jour

Rythme :

Date de dernière modification posologique : / /

Raison de demande :

Médicaments associés	Dosage	Rythme d'administration

NB : Pour l'INR : Le prélèvement est fait sur tube citraté 1V/9V.
Pour le génétique : Le prélèvement est fait sur tube EDTA (4ml de sang).

Figure 1: The follow-up sheet for patients on acenocoumarol.

The patient's drug prescriptions were collected using the follow-up sheet for patients on acenocoumarol. Figure1

2.5. Weighting of the risk level of interactions

In order to assess the level of risk of an interaction, a method of weighting interactions based on a model developed by Gschwind L et al for the prospective analysis of FMEA-type risk (analysis of failure modes of their effects and of their criticality) was used. This approach is based on pharmacological data (kinetics and dynamics) of drugs co-prescribed with acenocoumarol [5]. It consists of calculating the criticality index for each drug by multiplying three scores, the first score is based on the exact mechanism of the interaction, it varies from 1 to 10, The second score ranging from 1 to 10 concerned the frequency of occurrence of a supratherapeutic INR (≥6), finally the last score concerned the occurrence of a hemorrhagic accident. Drugs with the highest criticality indices (CI) are considered to be the drugs most at risk for bleeding or thrombotic complications when combined with acenocoumarol.

3. Results and discussion

3.1. Development of the acenocoumarol AMI database

Our literature search on drug interactions with acenocoumarol identified 376 drugs that may interact with acenocoumarol. The most incriminated families were anticancer drugs, antiplatelet drugs, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids (except hydrocortisone), low molecular weight heparins and related (curative doses and / or elderly), selective inhibitors of the reuptake of serotonin, mixed adrenergic-serotonergic drugs, androgens, enzyme-inducing anticonvulsants, cytotoxics, fibrates, HMG-COA reductase inhibitors (statins), protease inhibitors boosted by ritonavir and other drugs. These interactions have been compiled in an Acenocoumarol Interaction Log.

3.2. Characteristics of the study population

Table 1: Summary table of clinical and demographic characteristics of the study population.

Parameter	Variables	Low dose of acenocoumarol (≤17.5mg / week) n = 11	High dose of acenocoumarol (> 17.5 mg / week) n = 29
Age (years)	50.92	50.54	51.06
Sex			
Male	23	6	17
Feminine	17	5	12
Size (cm)	166.72	167.36	166.44
Weight (kg)	67.76	61.91	69.22
Body mass index	24.19	22.13	25.04

In our study, 40 patients treated with acenocoumarol were followed up at the EHU pharmacovigilance service in

Oran. The number of INRs measured was 421. INRs ≥ 4 represented (n = 40) 9.5% of total INRs, INRs ≥ 6 represented (n = 8) 1.9% of total INRs.

3.3. Analysis of drug prescriptions

One hundred and forty-two prescriptions were analyzed and 340 drug interactions were identified. A total of 853 drugs have been co-prescribed with acenocoumarol. Enoxaparin sodium and heparin calcium were not included in our study because they are prescribed in combination with acenocoumarol in several indications to overcome the latency period of acenocoumarol.

3.4. Medicines that interact with acenocoumarol

Based on the preestablished acenocoumarol drug interaction database, and out of a total of 68 INNs, 22 have been identified as potentially interacting with acenocoumarol. These drugs were co-prescribed 167 times with acenocoumarol representing 19.57% of the total co-prescribed drugs. The top ten co-prescribed drugs were: omeprazole (n = 51), amiodarone (n = 29), diclofenac sodium (n = 23), atorvastatin (n = 16), acetyl salicylic acid (n = 11), paracetamol (n = 10), levothyroxine (n = 10), indomethacin (n = 8), cetrizine (n = 5), ciprofloxacin (n = 5). Figure 1

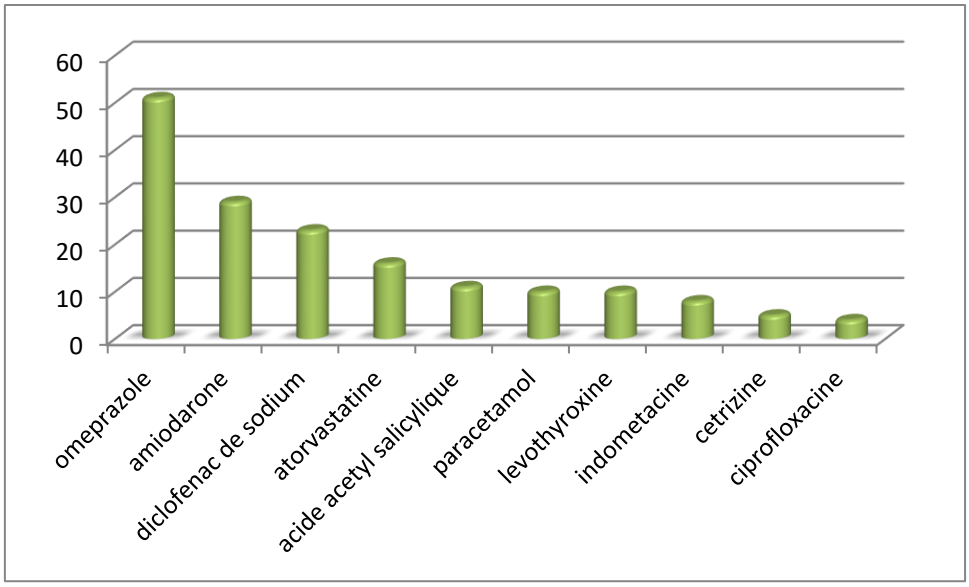

Figure 3: The drugs most co-prescribed with acenocoumarol

3.5. Mechanism of interactions

Of these interactions, 18% were pharmacokinetic interactions, 18% were pharmacodynamic interactions, 9% combined the two mechanisms and 55% were interactions whose mechanism is not well known.

Among the drugs with a pharmacodynamic interaction mechanism, we have found acetyl salicylic acid, cetrizine

and NSAIDs. Drugs with a pharmacokinetic interaction mechanism are represented by amiodarone, omeprazole, fluconazole and ciprofloxacin. Drugs which interact with both mechanisms are presented by diclofenac sodium and ibuprofen. Corticosteroids, antibiotics and paracetamol interacted with poorly understood mechanisms. Table 2

3.6. Relationship between interaction and supratherapeutic INR

In order to study clinically significant interactions, we looked for patients who presented with an INR≥6 (because INR≥6 is often associated with hemorrhagic manifestations). Eight supratherapeutic INRs were identified, in 62.5% of them we found that there was a drug interaction with acenocoumarol. Two drugs were implicated: amiodarone (n = 5), omeprazole (n = 1), these were pharmacokinetic AMIs (enzymatic inhibition).

3.7. Relationship between interaction and INR fluctuations

Fluctuations in INR were present in 57.7% of cases (n = 243), in 30% of them drug interactions were encountered. The drugs most implicated were: omeprazole (n = 36), amiodarone (n = 22), diclofenac sodium (n = 15), paracetamol (n = 8), indometacin (n = 8). Figure 1

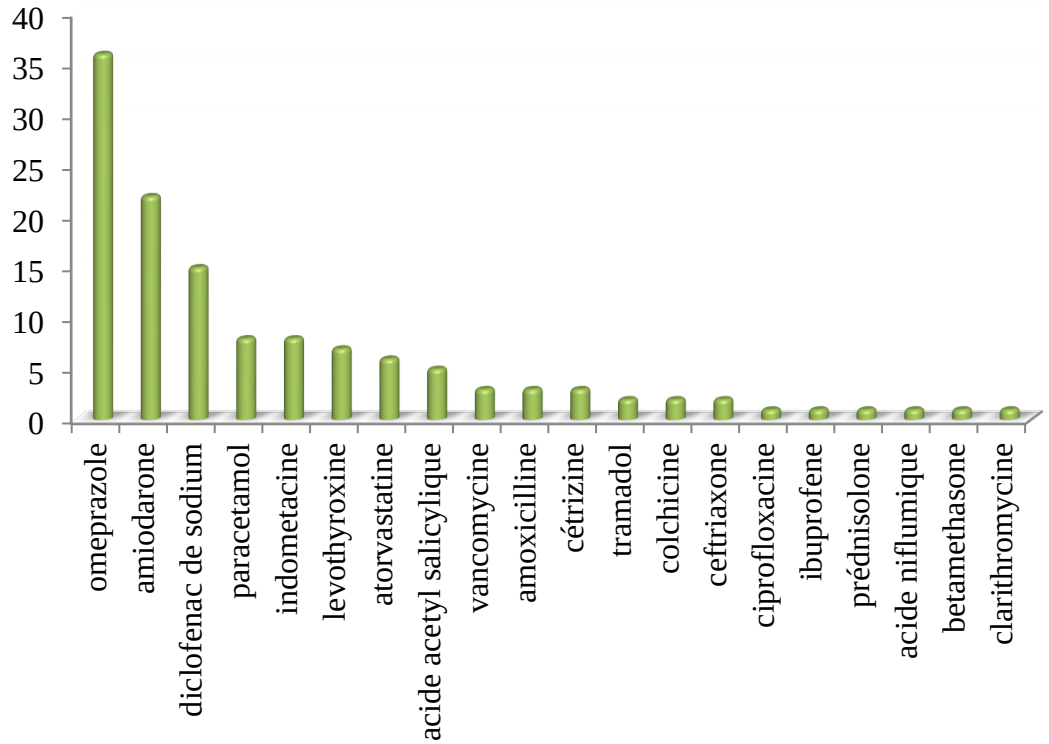

Figure 2: AMIs associated with a fluctuation in INR.

Table 2: Classification of drugs that interact with acenocoumarol according to their mechanism of interaction

Drug	Mechanism of interaction
Acetylsalicylic acid	Pharmacodynamic interaction
Niflumic acid	Pharmacodynamic interaction
Amiodarone	Pharmacokinetic interaction
Amoxicillin	Mechanism not well known
Atorvastatin	Mechanism not well known
Betamethasone	Mechanism not well known
Ceftriaxone	Mechanism not well known
Budesonide	Mechanism not well known
Cetrizine	Pharmacodynamic interaction
Ciprofloxacin	Pharmacokinetic interaction
Clarithromycin	Mechanism not well known
Colchicine	Mechanism not well known
Sodium diclofenac	Pharmacokinetic and pharmacodynamic interaction
Fluconazole	Pharmacokinetic interaction
Ibuprofen	Pharmacokinetic and pharmacodynamic interaction
Indomethacin	Pharmacodynamic interaction
Levothyroxine	Mechanism not well known
Omeprazole	Pharmacokinetic interaction
Paracetamol	Mechanism not well known
Prednisolone	Mechanism not well known
Tramadol	Mechanism not well known
Vancomycin	Mechanism not well known

3.8. Relationship between interaction and hemorrhagic events

In our study, bleeding events occurred in three patients, and required administration of vitamin K and red blood cell transfusions. Three drugs were implicated: omeprazole (n = 1), diclofenac sodium (n = 1) and amiodarone (n = 1).

3.9. Assessment of the hemorrhagic risk of interactions by calculating the criticality index

We considered drugs with a criticality index ≥10 (index chosen arbitrarily) to be the most at risk of interacting with acenocoumarol. Of the drugs tested, eight drugs had a criticality index ≥ 10, which are represented by the following drug classes: proton pump inhibitors, NSAIDs, antiplatelet agents, antifungals and amiodarone.

Consider the mechanism of the interaction, this was in 62.5% of the cases of pharmacokinetic interaction (associated with a pharmacodynamic mechanism for sodium diclofenac and ibuprofen) and in 37.5% of the

cases of pharmacodynamic interaction. Table 3

Table 3: Criticality indices of drugs interacting with acenocoumarol

DCI	Mechanism of interaction	Frequency of supratherapeutic INR	Frequency of bleeding event	Total score
Amiodarone	10	8	4	320
Omeprazole	5	3	4	60
Sodium diclofenac	10	1	4	40
Indomethacin	10	1	1	10
Acetylsalicylic acid	10	1	1	10
Ibuprofen	10	1	1	10
Niflumic acid	10	1	1	10
Fluconazole	10	1	1	10
Cetrizine	5	1	1	5
Ciprofloxacin	5	1	1	5
Paracetamol	1	1	1	1
Levothyroxine	1	1	1	1
Atorvastatin	1	1	1	1
Vancomycin	1	1	1	1
Amoxicillin	1	1	1	1
Tramadol	1	1	1	1
Colchicine	1	1	1	1
Ceftriaxone	1	1	1	1
Prednisolone	1	1	1	1
Betamethasone	1	1	1	1
Clarithromycin	1	1	1	1
Budesonide	1	1	1	1

3.10. Discussion:

Analysis of prescriptions from our study population revealed 340 drug interactions. 22 DCIs were responsible for these interactions. Indeed, two drugs have been implicated in the occurrence of a supratherapeutic INR, amiodarone (83%) and omeprazole (17%), this can be explained by the fact that on the one hand, amiodarone is a potent inhibitor of CYP2C9 the isoenzyme responsible for metabolism of the S-enantiomer of acenocoumarol and a large part of the R-enantiomer of acenocoumarol and omeprazole which is a potent inhibitor of CYP2C19 the responsible isoenzyme the metabolism of part of the R-enantiomer of acenocoumarol; and on the other hand, these two drugs are the most co-prescribed with acenocoumarol, which increases their frequency of involvement in the supratherapeutic INR. Based on the risk level of interactions weighting system, amiodarone was the drug

with the highest risk of clinical manifestations when interacting with acenocoumarol with a criticality index CI = 320. This interaction has been widely described in the literature, rigorous monitoring is therefore recommended during the use of this combination and given the long half-life of amiodarone (20 to 100 days) [6], and precautions should be taken and maintained for several weeks after stopping treatment. Omeprazole also had a high risk of interaction with acenocoumarol with a criticality index CI = 60. Omaprazole, which is often co-prescribed with acenocoumarol to prevent gatro-duodenal bleeding, is a potent inhibitor of CYP2C19 for this reason the INR should be followed closely in combination. Our results are similar to those published by Gschwind and al [5] which classify omeprazole with drugs at high risk of interacting with acenocoumarol. The observational study by Teichert and al [7] found that the risk of an increased effect of aenocoumarol when combined with omeprazole is less pronounced and not significant. Given the contribution of CYP2C19 only in R- metabolism and taking into account the short half-life of omeprazole (1 hour), it is considered that omeprazole can be prescribed without risk with acenocoumarol provided it is not not take them at the same time. The interaction between NSAIDs and acenocoumarol has been widely described in the literature, they increase the risk of bleeding through their ulcerative action on the gastric mucosa. Azole antifungals increased the hemorrhagic risk of acenocoumarol by enzymatic inhibition of CYP 2C9 and CYP 2C19, the enzymes responsible for the metabolism of acenocoumarol, this is in agreement with the study published by Schelleman and al [8] as well as study published by Becker and al [9], who found a significant increase in the INR when azole antifungals were combined with acenocoumarol, requiring a reduction of up to 50% of the dose of acenocoumarol administered according to the study made by Lozano and al [10]. Acenocoumarol does not increase the effect of acetylsalicylic acid but interferes with its antiplatelet action. On the other hand, in our study, tramadol and antibiotics were not involved in the occurrence of hemorrhagic events with acenocoumarol, unlike studies carried out by Penning-van beest F, and al. [11], Schelleman and al [8] and Gschwind and al [5] which show that these drugs are at high risk of bleeding, this can be attributed to the fact that in our case it is a single-center study which s 'is interested only in patients hospitalized at the EHU of Oran as well as the non-use of tramadol for analgesic purposes in order to avoid its interaction with acenocoumarol.

4. Conclusion:

Given that the clinical consequences linked to drug interactions are often unrecognized and sometimes lead to inappropriate therapeutic attitudes. It therefore seemed advisable to us to study the drug interactions of acenocoumarol in order to improve the quality of the prescription and the safety of use of acenocoumarol.

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