Universitat Autònoma de Barcelona

DOCTORAL THESIS

Monitoring and analysis of adverse reactions associated with medicines recently approved for treatment of cardiovascular disease collected through the spontaneous reporting system

Seguimiento y análisis de reacciones adversas a fármacos de reciente comercialización para el tratamiento de patología cardiovascular reportadas mediante notificación espontánea

Mónica Natalie Tarapués Román

Thesis Director: Dr. Albert Figueras

Universitat Autònoma de Barcelona
Departament de Farmacologia, de Terapèutica i Toxicologia
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Mónica Natalie Tarapués Román

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To all people interested in drug safety

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Abstract

Several medicines for treatment of cardiovascular disease and other risk factors such as diabetes, dyslipidemia, and hypertension are available in the market. However, at the moment of drug approval, the safety profile should be considered provisional due to the limitations of the pre-marketing clinical trials. Also, relevant safety information about newly launched medicines usually arises in the first post-marketing years. The aim of this thesis is to contribute to the knowledge regarding safety profile of new marketed cardiovascular drugs using reports collected in the Spanish spontaneous reporting system. A group of cardiovascular drugs launched in Spain between 2007 and 2011 was selected. All the spontaneous reports involving the study drugs until the end of 2014 were retrieved and carefully analysed. Also, a review of case reports published and other scientific information was done. Statistical methods were applied to strengthen the potential ADR-drug associations. The main results were described in two original studies. In study I, an association between gliptins use and musculoskeletal reactions was found in the Spanish database. Gliptins are a new antidiabetic class that inhibits the action of dypeptidil peptidase-4 enzyme for controlling the glucose blood level in type 2 diabetic patients. In May 2012, thirty-four reports describing musculoskeletal complaints with gliptins were found in the database; twenty-seven for sitagliptin, six for vildagliptin and one for saxagliptin. These cases represented the 10% of all gliptins reports. Moreover, in two of them positive re-exposure was described. These adverse reactions were hardly described with gliptins use. Despite not being serious, these symptoms may impair the treatment adherence in patients with type 2 diabetes. In study II, the potential association between the use of dronedarone and renal impairment was analysed. The effect of dronedarone on renal function was supported by limited information. Dronedarone, a new antiarrhythmic drug, is a noniodinated amiodarone derivative indicated for the treatment of atrial fibrillation. In the Spanish database ten cases were found and, in addition, eight cases were identified in medical literature. These eighteen cases described renal impairment during dronedarone treatment. All cases showed a plausible temporal association, although the baseline conditions could be considered as potential confounder. Renal impairment associated with this drug could seriously aggravate the clinical condition of patients with atrial fibrillation, especially in those who also suffer from heart failure. Despite the fact that, either in musculoskeletal reactions associated with gliptins or renal impairment with dronedarone, further observational studies are needed in order to verify these potential safety signals, in the meantime clinicians should be aware of these potential reactions in clinical practice. The knowledge of safety information of marketed medicines is a constant process that is built-up over time. Pharmacovigilance was the first method for post-marketing surveillance and despite its inherent limitations such as lack of information or underreporting, it still contribute to the main objectives of post-marketing surveillance: to increase patients' safety and to decrease the prescribers' euphoria in front of new medicines.

CONTENTS

LIST OF ABBREVIATIONS

ADRs	Adverse drug reactions
AF	Atrial Fibrillation
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FDA	Food and Drugs Administration
FAERS	FDA Adverse Event Reporting System
FEDRA	Farmacovigilancia Española Datos de Reacciones Adversas
HbA1c	Glycated Haemoglobin A1C
IC	Information Component
PRR	Proportional Reporting Ratio
RCT	Randomized control trials
ROR	Reporting Odds Ratio
SDR	Signal of Disproportionate Reporting
SPC	Summary of Product Characteristics
SPvS	Spanish Pharmacovigilance System
US	United States
WHO	World Health Organization

1. Introduction

1.1 General Overview

The last decade, cardiovascular disease (CVD) accounted for nearly half of non-communicable diseases. This increase in chronic diseases has attracted the attention of medicine-industry, thus, many new active ingredients are constantly put into the market.

1.1.1 Cardiovascular disease

CVD is considered a relevant problem in public health; in 2012 it was the leading global cause of death, accounting for 17.3 million deaths around the world, a number that is expected to grow to >23.6 million by 2030. CVD continues to cause a much greater mortality burden among Europeans than any other disease. CVD caused 51% of deaths among women and 42% among men in 2013, compared with 19 and 23%, respectively, for all cancers (1).

CVD is a broad term for a range of diseases affecting the heart and blood vessels. CVD affects not only high-income but also low and middle-income countries. It is estimated that in 2030 in the world, the leading causes of death will be ischemic heart disease and cerebrovascular disease, both components of CVD (2,3). CVD risk is most frequently the result of multiple interacting risk factors involving demographic characteristics, family history of CVD, smoking, physical inactivity, dyslipidemia, obesity, hypertension and diabetes.

Several risk factors in one patient give rise to multimorbidity, and this consequentially generates another health problem: polypharmacy, especially in elderly people (4). Type 2 diabetes mellitus (T2DM) is a prevalent disease across the European Union (EU), it has increased rapidly over the last ten years and this increase was around 50% in many countries, as well as an increase in the consumption of antidiabetic drugs (5,6). Thus, CVD prevention should be considered in all patients with one or more cardiovascular risk factors. Currently there are several risk scores for prediction of CVD. Developing a general applicable risk score is difficult because of confounders associated with ethnicity, cultural differences and metabolic markers, despite this, current risk scores are useful methods in clinical practice (7).

The health burden of CVD as well as other chronic diseases is accompanied by a significant deleterious economic impact. Overall CVD is estimated to cost the EU economy almost €196 billion a year. About half of this total cost (54%) is related to health care costs, 24% due to productivity losses and 22% due to the informal care of people with CVD (5). The median numbers of hospital discharges per 100,000 population in 2012 were 2,097 for CVD, 608 for coronary heart disease, and 298 for cerebrovascular disease (1).

The clinical approach to prevention and/or management of CVD is complex. In general, it is recommended non-pharmacological treatment (i.e. adequate physical activity, healthy eating habits, avoid tobacco, and reduction of overweight), pharmacological therapy, and in some cases surgical procedures. Regarding pharmacological therapy, it includes treatment of basal risk factor such as diabetes, hypertension, dyslipidemia, as well as other pharmacological strategies for primary prevention of CVD. Nowadays, several pharmacological options are available in the market, and also many new drugs have been approved around the world in the last decade.

1.1.2 Post-marketing drug life cycle

Clinical trials in preapproval phase (phases I, II and III) are mainly designed for assessing drug efficacy but are much less effective for evaluating safety. Post-marketing studies (phase IV) are focused on patient safety, and are usually carried up by the pharmaceutical industry.

Newly approved medicines are often marketed and promoted as products with more clinical efficacy and safer than the older pharmaceutical options. In clinical practice, the physicians should perform a risk-benefit assessment at individual level before each prescription. Notwithstanding this, in the case of new active ingredients the rational selection process is especially difficult because most relevant safety information arises in the first post-marketing years, thus the risk-benefit assessment should be done carefully.

It is well known that the patients included in the randomized control trials (RCT) are different from the patients found in the real clinical practice. RCT have potential concerns in terms of safety, such as limited heterogeneity of patients (i.e. exclusion of geriatric patients, paediatric population, etc), short period of exposure to the drug, and also the limited sample size to detect rare adverse drug reactions (ADRs) (8,9).

Therefore, the information available at the moment of the approval is incomplete, and the safety of new drugs should be considered provisional. Despite this, there is a common misconception that drug development life cycle ends when the drug reaches a place in the market. Indeed, post-marketing surveillance, dependent or independent from pharmaceutical industry, is essential to get a better knowledge about safety of drugs in the market.

In general, post-marketing surveillance contributes to the knowledge of drugs in different populations. In real life settings the new drug is used in different doses and routes of administration, with longer time of exposure, and potential off-labelled uses. Post-marketing surveillance allows to evaluate the whole profile of medicines including undiscovered and rare ADRs, additional information regarding contraindications, precautions, drug-drug interactions, and in some cases the risks and benefits of off-labelled uses (9–11)

1.1.2.1 Drug withdrawals

There have been cases of medicines that had to be withdrawn only 1 or 2 years after their launching for safety reasons. These drug withdrawals are reminders of the complex process of post-marketing drug surveillance (12,13). The following examples of drug withdrawals are just some of the most talked-about cases in the last 15 years, and help to point out the relevance of post-marketing surveillance in order to protect the population.

Cerivastatin was launched in the EU in 1997 as the newest statin in the market. This drug belonged to the group of inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase. Cerivastatin was metabolized by CYP450, thus drug-drug interactions were considered as a potential concern. Two years later, a contraindication of concomitant prescription of cerivastatin and gemfibrozil was added to the Summary of Product Characteristics (SPC). In 1999 the first case report of rhabdomyolysis associated with cerivastatin and gemfibrozil was published (14). The Medicines Regulatory Agency in Spain as well as in other countries announced safety alerts in order to warn clinicians about contraindications and precautions with the use of cerivastatin. Despite this, many cases of rhabdomyolysis were reported to the national programs; some of them with fatal outcomes. Several countries suspended marketing and distribution of cerivastatin. Finally, in August 2001, the manufacturer of cerivastatin announced the worldwide withdrawal of cerivastatin from the market (15).

Sibutramine was a modulator of norepinephrine and serotonin that could reduce the food intake. This medicine was launched in 1999 in the EU for the management of obesity. In 2002, the Italian regulatory agency decided to cancel the marketing of sibutramine, because of several cardiovascular serious and fatal events that were reported to the Italian spontaneous reporting system. Also, some observational studies found an association between enlargement of QT interval and sibutramine use. Therefore, a contraindication of use of sibutramine in patients with high cardiac risk was included in the SPC. However, in 2010 the Sibutramine Cardiovascular Outcomes Trial (SCOUT) confirmed a higher risk with the sibutramine group compared with the placebo group. In September 2010 sibutramine was withdrawn due to high cardiovascular risk (16).

Rofecoxib was the first coxib launched in 1999; it was promoted as a new anti inflammatory drugs sub-group that was called “coxibs”. The first therapeutic indication or rofecoxib was osteoarthritis and later on, acute pain. In 2000, the results of the Vioxx Gastrointestinal Outcomes Research

(VIGOR) study were published, and its findings raised up concerns related to cardiovascular events associated with rofecoxib use. However, this excessive number of cardiac events was justified due to the cardioprotective mechanism of the naproxen (control group). So, despite these concerns, rofecoxib remained in the market and regulatory agencies only recommended adherence to the specific indications and being aware of the contraindications and precautions. Reports from spontaneous reporting were also published (17). Few years later, additional analyses of the VIGOR trial confirmed the higher risk of cardiovascular events with rofecoxib, and more or less at the same time other two clinical trials were stopped for the same risk of rofecoxib: the APPROVe trial (Adenomatous Polyp PRevention On Vioxx), and the VICTOR trial (Vioxx in Colorectal Cancer Therapy: definition of Optimal Therapy). The cardiac risk associated with rofecoxib generated several discussions among the medical community, academia, and regulatory authorities (18,19). Finally, rofecoxib was suspended from the worldwide market in September 2004 (20,21).

Rosiglitazone was a thiazolidinedione antidiabetic agent; its mechanism of action was predominantly the modulation of the peroxisome proliferator-activated receptor-γ (PPARγ) receptor and the stimulation of insulin sensitivity. It was launched in Europe in 2000. The principal concern at the moment of commercialization was fluid retention and oedema associated with its use. In the early years of post-commercialization another significant concern was the potential for liver toxicity. Also, a review from the spontaneous reports in Canada pointed out few fatal or serious cases associated with the use of rosiglitazone (22). In Europe as well as in the US, a benefit/risk analysis was started in order to consider the safety use of this drug. In 2007, a metaanalysis showed a higher risk of myocardial infarction associated with rosiglitazone. In 2010 the final analysis of the RECORD trial (Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes) confirmed an increased risk. In the light of the published information, the EMA considered to withdraw rosiglitazone from the market due to a high risk of cardiovascular serious events (23).

Market withdrawal is the latest and the hardest decision to protect the population from medicines harm. During the lifecycle of a given drug many strategies are carried out in order to detect safety problems in post-marketing settings. Despite these efforts, some of the safety issues were undetected in randomized control trials (RCT), and sometimes this is accompanied by a lack of transparency in pre-approval evidence. Anyway, some cases have been benchmarks for the health-care community and researchers in terms of public health and careful use of drugs.

1.1.3 Adverse drug reactions

In 1972, an ADR was defined by the World Health Organization as “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function” (24).

However, this term has changed over the time and along with the activities related to post-marketing surveillance. In 1995 a subtle clarification regarding the definition of ADR was included in the International Conference Harmonisation. Therefore, it was added the definition of ADR in the pre-approval stages as "*all noxious and unintended responses to a medicinal product related to any dose..."* (25).

Later on, in 2010 a new European legislation was set up and started to come into effect in 2012 for all member countries. It was the most relevant change in the legislation since 1995; this change expanded the previous definition. Thus, "any noxious and unintended response included the use outside the terms of the marketing authorization, overdose, off-label use, misuse, abuse and medication errors" is also considered an ADRs (26).

In addition to the changes and improvements in the ADR definition, there is confusion regarding adverse drug reactions and adverse events. These terms are ordinarily used as synonyms or interchangeable words, but they have a slight difference worthy to mention. An adverse event is defined as any untoward event while a patient is taking a drug treatment regardless of the association with the pharmacological treatment (e.g., a car accident or fall); this term is commonly used in clinical trials.

Moreover, an ADR -complementing the definitions above- should be considered as any symptomatic or clinical expression of harm in a patient, in which a possible relationship between the clinical condition and the previous use of the medicines can be established with a causality assessment. There are other terms that could generate confusion, such us adverse effects or side effects. An explanation of the difference among these other terms can be found elsewhere (27,28).

The clinical and economic burden of ADRs is difficult to estimate at a global level. However, it has been estimated that ADRs account for 2.5 to 10.6% of hospital admissions in Europe (9). A systematic review of prospective observational studies found that higher rates of hospital admissions associated with ADRs were presented in patients with multiple medications for chronic diseases. It is important to highlight that cardiovascular drugs are one of the most frequent pharmacological groups associated with ADRs admissions in adults and elderly patients (29).

Medicines safety is a continuous process built over time; certainly there are many stakeholders involved, but health-care professionals, as well as clinical researchers play a crucial role in the whole process. In this context, indubitably pharmacovigilance is one of the most traditional activities which, despite its limitations, it has contributed to draw the safety profile of new drugs.

1.1.4 Pharmacovigilance

Pharmacovigilance is defined as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems” (30).

Pharmacovigilance has several methods in order to detect these problems related with the use of medicines Thus, active pharmacovigilance includes studies of prescription event monitoring or intensive review of potential ADRs in hospital admissions or discharges (electronic medical records databases) among others.

On the other hand, passive pharmacovigilance rely mainly on spontaneous reporting. The health-care community is encouraged to report any suspicion of ADRs observed in clinical practice to the pharmacovigilance system. Recently, more complex methods of data mining have been developed especially in electronic medical records and claim databases.

Some of these methods are considered as pharmacoepidemiological tools. Pharmacoepidemiology is the science that studies the use and the effects of drugs on a large number of people, and this science is crucial for the post-marketing evaluation of drugs in the population (31).

Pharmacoepidemiology and pharmacovigilance are complementary new sciences that have changed in the last decades; mainly because of the evolution of epidemiological methods and the changes in the definition of ADRs, or the variation of marketing and promotional techniques (28,32,33).

Among the methods in pharmacovigilance, spontaneous reporting is the most traditional and is considered the cornerstone for post-marketing surveillance. It is a useful method for generating hypotheses regarding drug safety. These hypotheses can be analysed and verified with additional pharmacoepidemiological studies.

Spontaneous reporting has well known limitations such as underreporting, lack of information and biased reporting, among others (33,34). In spite of these drawbacks, this method is still used worldwide. Its relevance lays on the suspicion of ADRs sent by the clinicians and the analysis and evaluation made by qualified physicians, clinical pharmacologists and pharmaceutics.

1.1.4.1 Pharmacovigilance historical background

Before 1950, the importance of post-marketing surveillance for new medicines was not considered as a commitment that should integrate each physician, patients and lawmakers as nowadays. In those times, in the US, cases of aplastic anaemia associated with chloramphenicol were the trigger for the first steps to register and control the use of medicines. However, the

emerging Food and Drug Administration (FDA) did not collect adverse events observed once the medicines were launched to the market.

In 1962, the disaster of phocomelia associated with thalidomide was an eye-opening situation for the world about the importance of drug surveillance in clinical practice. Thalidomide was commercialized in several countries under many trade names and indicated for several therapeutic conditions. Phocomelia associated with thalidomide awoke the interest of all medical community and the governments around the world; for instance, the United Kingdom started a spontaneous reporting system called the "yellow card" scheme. Similar activities were started in other countries such as Canada, Norway, Sweden, and Denmark in order to strengthen the patients' safety and public health.

In 1968, the WHO created the international programme of drug monitoring; this project started with 10 member countries (27). Since 1978 the international programme is based in the Uppsala Monitoring Centre in Sweden, and the reports of each member country are collected in an international database. Nowadays, 131 countries are part of the international programme, and more than 8 million of reports are gathered in the WHO database -VigiBase-.

1.1.5 Causality Assessment in pharmacovigilance

Causality assessment is defined as an evaluation of the likelihood that a medicine was the causative agent of observed ADRs. Causal relationship intends to establish a relation between an event A (in pharmacovigilance; the medicine), and an event B (the ADR), in which A precedes and causes B. This association is difficult to establish and depends on the available information.

Causality assessment is usually performed with the aid of algorithms. In some countries, pharmacovigilance is established as a national program and causality assessment has been adapted as a routine activity (35,36). This assessment is not a conclusive evidence of association, and there is a level of uncertainty that it is worth to bear in mind. Despite this, causality algorithms by some means categorize the potential association between the suspected drug and the ADR.

Many algorithms have been developed to categorize in a semiquantitive way the causality association. The basic criteria of evaluation are based on time association, previous knowledge of the ADRs, biological o medical plausibility, and likelihood or exclusion of other cases. The strongest causality criterion is the re-challenge or re-exposure to the same drug in different periods of times and at best under the same conditions. Nevertheless, this is difficult to assess especially for ethical reasons in serious or fatal events. The final score obtained from the addition of the points for each criterion permit to classify the report into categories of association.

Depending of the score, the most common ones are: certain, probable/likely, possible, unlikely, conditional/unclassified and unclassifiable.

There is not a gold standard among the causality assessment methods due to the lack of consistency and reproducibility. A systematic review found thirty-four methods; 27 algorithms, 4 expert's judgement/global introspection, and 4 probabilistic methods (37). These methods neither eliminate nor quantify uncertainty, but categorize the potential association. Each tool has advantages and disadvantages, the main concerns with these methods are the poor reproducibility and the inter-rater/intra-rater disagreements. Anyway, the consistent use of an algorithm helps to the homogeneity of evaluation of the different reports in a given pharmacovigilance centre.

In pharmacovigilance, the causality assessment has its first step at individually level. Each spontaneous report is evaluated with a specific algorithm in order to categorize the causality association of the ADRs reported with the suspected drug(s). A second step is done in order to perform an interpretation of the aggregated date, (a specific or group of ADRs with a determined drug). The latter step is only completed for a minority of case reports, when actions or measures are deemed necessary and this process takes part in the signal detection. However, at individual level or at aggregated, the causality is provisional; it depends on the current knowledge of the drug and the available information.

1.1.6 Signal detection

The WHO has defined a signal as "reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously" (38). Also, a signal is an association that is considered important to investigate further. A signal may refer to new information on an already known association (28).

In pharmacovigilance more than a single report is required to generate a signal, depending on the seriousness of the event and the quality of the information. The traditional qualitative method is the case-by-case. In this method a cluster of reports often attracts attention of regulatory agencies or researchers, due to either the relevance or seriousness of the ADRs or also because the reactions are unknown for a new drug. These cases will be evaluated in detail in order to provide new information regarding the potential association between the drug and the ADR. Sometimes this group of reports can be separated in a core minority of well-documented cases for the causality assessment (called "indexes cases"), and a larger number of reports of lower quality ("feasible cases"). The aggregated causal assessment is a complex evaluation that requires clinical and pharmacological expertise (35,39,40).

Also, there are quantitative signals, which are based on the use of computational or statistical methods for identify drug- event pairs in databases. These signals are supported not just in clinical

information; they are based on disproportionality measures that help to support the hypothesis. They are called signals of disproportionate reporting (SDR) (40).

These disproportionality measures are statistical approaches that can be divided in two groups. The first group, the frequentist methods are used by many regulatory agencies as a routine signal detection method. The main measures are: Proportional Reporting Ratio (PRR), used by the EMA and the Italian agency, and the Reporting Odds Ratio (ROR) used by the Netherlands and Spain. Furthermore, the Bayesian methods such as the Information Component (IC) are used by the WHO, and the multi-item Gamma Poisson Shrinker, by the FDA. The latter ones are more complex statistical approaches and they were developed for bigger databases (41).

Signal detection in pharmacovigilance is considered an activity for hypothesis generation. These hypotheses might generate additional larger and especially designed studies to verify the relationship. In some cases, this signal is enough for a preventative suspension of the drug commercialization or even its definitive withdrawal. In other cases, the signal means the beginning of more specific studies. Notwithstanding, while these studies are carried out, it is very important that the medical community know the potential association of the drug-event and be aware of the appearance of new cases.

By now, spontaneous reports databases are not considered the unique source of information for signal detection. The new data mining techniques have been used for pharmacoepidemiological objectives, especially for post-marketing surveillance (i.e. electronic medical records, claim databases). Moreover, another source of information that could enrich signal detection is case reports published in medical literature. Despite the current recommendation of publishing case reports after being notified to the respective national pharmacovigilance system, it is still possible to find few cases that are not reported to the national centres. The review of the medical literature is of special interest in the case of newly market drugs (42).

1.1.7 The Spanish Pharmacovigilance system

In Spain, the first law in order to regulate and control medicines was released in 1973; however, it was only in 1982 when it was set up a research project between the Universitat Autònoma de Barcelona and the Vall d'Hebron Universitary Hospital for setting up a local pharmacovigilance program. Later, in 1983 the Spanish Health Ministry decided to expand this programme to the national territory and assumed its leadership. At present the Spanish pharmacovigilance system (SPvS) is consists of 17 regional centres (one centre for each autonomous community). Since the early stages of the programme, spontaneous reporting was considered as a cornerstone method. Yellow card scheme was implemented and strengthened in order to uncover safety issues that could threaten patients' health. According to the current pharmacovigilance law, health-care professionals (physicians, nurses or other health-care personal) are obligated to report any

suspicion of adverse drug reaction. Also, the pharmaceutical industry has to report all the suspicions of adverse events associated with its medication (43,44).

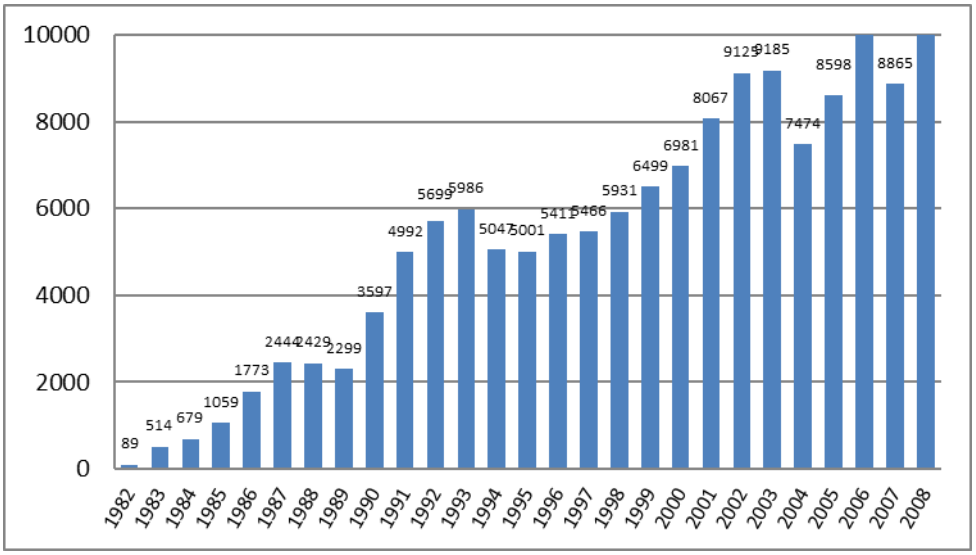

Figure 1 FEDRA database by year. Total reports in the database: 141,632. Reproduced from: Manso G, Hidalgo A, Carvajal A, de Abajo FJ. El Sistema español de farmacovigilancia de medicamentos de uso humano. Su historia en cifras. In: Los primeros 25 años del Sistema Español de Farmacovigilancia de Medicamentos de Uso Humano. Madurga M, Lázaro F, Martín-Serrano G, Quiroga MC, 1st edn. Oviedo: Universidad de Oviedo Publisher, 2010: 32

All spontaneous reports are gathered in the national database called “FEDRA” (for its Spanish meaning: Farmacovigilancia Española. Datos de Reacciones Adversas). Also, FEDRA contains ADRs found by special intensive monitoring or other specific studies.

In the SPvS each report is undergone to a modification of the Karch y Lasagna causality algorithm. This Spanish algorithm has five components: compatible temporal sequence, previous knowledge of ADR, withdrawal effect or dechallenge, rechallenge or re-exposure, and evaluation of alternative causes (45,46). All the reports included in FEDRA are carefully analysed and evaluated with this algorithm.

In 2008 FEDRA contained about 140,000 reports; every year roughly 8,000 reports are added to the FEDRA database. Figure 1 describes the annual number of reports registered in the database.

2. Hypothesis and Aims

2.1 Hypothesis

Relevant information and concerns about the safety of new drugs in the market arises during the first post-marketing years. The marketing of cardiovascular medicines is a very dynamic process; hence, intensive monitoring and the analysis of spontaneous reports of new cardiovascular drugs could contribute to the information building-up process for enhancing the safety knowledge of this group of medicines.

2.2 Aims

The overall purpose of this thesis was to contribute to the knowledge regarding the safety profile of new drugs launched to the market for the treatment of cardiovascular diseases using the spontaneous reports gathered in the Spanish Pharmacovigilance System.

The specific objectives were:

Study I

- To describe the reports of musculoskeletal adverse drug reactions in patients exposed to any gliptin (sitagliptin, vildagliptin and saxagliptin).
- To assess the association between gliptins use and adverse drug reactions.

Study II

- To analyze the clinical information supporting the association between dronedarone use and renal impairment.
- To search other case reports published in medical literature in order to analyze the characteristics and point out the relevance of the adverse reaction.

3. Methods

3.1 Selection of study medicines

All news drugs approved for treatment of chronic cardiovascular diseases by the Spanish Agency of Medicines and accepted by the National Health System between January 2007 and December 2011 were identified. These drugs can be classified in 5 pharmacological groups: antidiabetics (sitagliptin, vildagliptin, saxagliptin, liraglutide y exenatide) anticoagulant/antiagregrant (dabigatran, rivaroxaban, apixaban, cilostazol, prasugrel), statins (rosuvastatin, pitavastatin), and other cardiovascular medicines (aliskiren, ivabradine, ranolazine, dronedarone).

3.2 Database and Data Management

Every six months, all spontaneous reports involving the study drugs were retrieved from the SPvS database (FEDRA) and analysed to seek new combinations of potential ADRs (17 selected cardiovascular drugs). In order to identify new potential associations ADRs-medicine a careful qualitative and quantitative examination was done. In exceptional cases, the reporter was contacted for additional information. The qualitative analyses were focused on searching possible ADRs-drug relationship (demographic, clinical and pharmacological features).

The datasets with information about spontaneous reports with each drug were downloaded to an Excel file. A depuration process was made in order to sort out the data. After that, the information was processed with the SPSS® 19 software.

In order to know he pre-approval and post-marketing history of the study medicines, the European public assessment report (EPAR) for each drug was reviewed at the European Medicine Agency website. The EPAR was taken as an initial point of information (special importance was paid to the “risk management plan”). At the same time, a comprehensive revision of the changes in the SPC of each drug was also done.

In the relevant ADR-medicines combinations, an exhaustive search in Pubmed and other medical literature resources was done. All the published case-reports or other related scientific articles were evaluated for either strengthen or weaken our findings of potential new associations of ADRs-drugs.

3.3 Statistical Analyses

For descriptive variables, χ^2-test was used, and student's t-test for numerical variables. For a new signal detection in FEDRA database, there were needed at least 3 new cases of the specific ADR and a statistical disproportionality method was applied.

The Reporting Odds Ratio (ROR) was used as disproportionality measure. In fact, the Proportional Risk Ratio (PRR) was also computed, however, ROR was considered as a selected measure. Sensitivity analyses were done in some cases in order to strengthen the findings. The comparator was the chemical predecessor of the new drug or other medicines with similar mechanism action.

Below are short summaries of the methods used in each study. The complete description of the methods will be found in each individual study (see results section).

Study I

- All spontaneous reports with musculoskeletal disorders associated with gliptins (sitagliptin, vildagliptin, a saxagliptin) were gathered and analyzed in the Spanish pharmacovigilance database since each gliptin was launched until May 2012.

- The ROR was the disproportionality measure taken.

Study II

- In the Spanish Pharmacovigilance database, reports with renal reactions and dronedarone until May 2014 were retrieved and analyzed.

- A statistical approach with the ROR as the disproportionality measure was done.

- Also, a review of case reports published on renal failure and dronedarone was conducted in MEDLINE.

4. Results

4.1 Association of musculoskeletal complaints and gliptin use: review of spontaneous reports.

Tarapués M, Cereza G, Figueras A.

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Association of musculoskeletal complaints and gliptin use: review of spontaneous reports

Mónica Tarapués[1]*, Gloria Cereza[1,2,3] and Albert Figueras[1,2]

[1] *Pharmacology, Therapeutics and Toxicology Department, Universitat Autònoma de Barcelona, Bellaterra, (Cerdanyola del Vallès), Spain*
[2] *Fundació Institut Català de Farmacologia, Passeig Vall d'Hebron, Barcelona, Spain*
[3] *Catalan Centre of Pharmacovigilance, Barcelona, Spain*

ABSTRACT

Purpose Gliptins are new oral antidiabetic drugs that increase insulin levels through dipeptidyl peptidase-4 inhibition. Recently, the association of serious musculoskeletal (MSk) adverse effects with the gliptin use has been suggested. The aim is to describe and analyze the characteristics of spontaneous reports related to these adverse effects and gliptin use.

Methods All spontaneous reports with MSk disorders associated with gliptins gathered in the Spanish pharmacovigilance database until May 2012 were described and analyzed using a case/non-case method.

Results Gliptins were reported as the suspected drug in 332 cases: 208 involved sitagliptin, 115 vildagliptin, and nine saxagliptin. In 34 patients (10.2% of total reports with gliptins), MSk reactions were described (22 women [64.7%] and 12 men [35.3%]). Their mean age was 65.1 years; 41.2% were younger than 65 years. Only seven cases were serious, but the gliptin had to be withdrawn in 22 patients because of intolerance and/or persistence of MSk discomfort, and patients recovered after its discontinuation. A positive re-challenge was observed in two cases. In seven cases, the patients were on previous chronic treatment with statins, and began to present MSk complaints shortly after starting a gliptin. The reporting odds ratio (ROR) for myalgia and arthralgia were strongly associated with gliptin use (ROR 1.96 [95% CI 1.12–3.43], $p < 0.05$ and ROR 2.69 [95% CI 1.38–5.24], $p < 0.05$, respectively).

Conclusions Musculoskeletal disorders are adverse reactions strongly associated with gliptins that, despite not being serious, may impair the treatment adherence in patients with type 2 diabetes. Future observational studies could confirm these findings.

KEY WORDS—type 2 diabetes mellitus; dipeptidyl peptidase-4 inhibitor; pharmacovigilance; drug utilization; spontaneous reporting system; pharmacoepidemiology

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INTRODUCTION

The inhibition of dipeptidyl peptidase-4 (DPP4) by the new oral antidiabetic drugs "gliptins" blocks the degradation of incretins such as glucagon-like peptide-1, thus stimulating insulin secretion from pancreatic β cells and decreasing glucagon release from pancreatic α cells.

The safety profile of gliptins suggests a good tolerability, but severe adverse drug reactions (ADRs) such as pancreatitis or upper respiratory infections have been associated with gliptin use[1,2]. Serious cases of rhabdomyolysis and synovitis have also recently been published.[3–6] The musculoskeletal (MSk) toxicity of the DPP4 is poorly understood, and there is an uncertainty about the possible association of these ADRs and gliptins.

Spontaneous reporting systems are effective for the early detection of safety signals and the generation of causality hypotheses especially during the first postmarketing years of drugs. The present study aims to describe the reports of MSk ADRs in patients exposed to any gliptin received by the Spanish Pharmacovigilance System (SPvS), and assess the association between gliptin use and MSk ADRs.

METHODS

The SPvS began its activities in 1982. Since then, it has received spontaneous reports of suspected ADRs from health care professionals and the pharmaceutical

*Correspondence to: M. Tarapués, Pharmacology, Therapeutics and Toxicology Department, Universitat Autònoma de Barcelona, E-08193 Bellaterra (Cerdanyola del Vallès), Spain. E-mail: mtr@icf.uab.cat

industry. We reviewed the SPvS database from the date sitagliptin was marked in Spain (March 2007) until May 2012, and analyzed all the spontaneous reports associated with the use of gliptins (sitagliptin, vildagliptin, or saxagliptin) and MSk ADRs. The MedDRA® (Medical Dictionary for Regulatory Activities; Maintenance and Support Services Organization, McLean, Virginia, USA) was used to identify MSk disorders. All cases with MSk complaints as part of another systemic process were excluded.

All variables contained in the standard report were analyzed: (i) demographic characteristics; (ii) ADRs description, onset and ending reaction dates, severity, and outcome; and (iii) onset and ending drug treatment dates for each medicine taken before the ADRs onset time, latency period (time elapsed between treatment onset and ADRs onset), information about drug withdrawal, re-challenge, and alternative causes that could explain the ADR.

To assess the association between gliptins and MSk reactions, the method case/non-case was used, and the reporting odds ratio (ROR) as measure of disproportionality was calculated[7]. The reports submitted with the most frequent MSk ADRs (myalgia, pain in extremity, and arthralgia) were considered as cases; the remaining reports with other ADRs were non-cases. The ratio cases/non-cases with gliptin use was compared with the ratio cases/non-cases for all other drugs. A separate analysis was made with other oral antidiabetic drugs. The analyses were conducted using SPSS 19.0 statistical software (IBM Corporation. Armonk, New York. USA).

RESULTS

Up to 332 spontaneous reports of ADRs attributed to gliptins (208 involving sitagliptin, 115 vildagliptin, and nine saxagliptin) were received. Thirty-seven reports described MSk ADRs; three cases were excluded because the MSk complaints were symptoms related to a systemic disease. The final sample with MSk reactions included 34 reports (involving sitagliptin [27], vildagliptin [6], and saxagliptin [1]). These 34 reports represented 10.2% of all gliptin reports. No differences in the distribution of demographic characteristics between patients with MSk and those with other ADRs were found. There were 22 women (64.7%) and 12 men (35.3%) with a mean age of 65.1 years (range: 44 to 81); interestingly 14 patients (41.2%) were younger than 65 years. In 27 cases, the ADRs were mild, and only seven were serious. Although no patient was hospitalized as a consequence of ADRs, the gliptin had to be withdrawn in 22/34 patients because of intolerance and/or persistence of the ADR (Table 1).

The 34 reports described 45 MSk ADRs that included myalgia (13 cases), pain in extremity (10), arthralgia (nine), muscle weakness (four), joint stiffness (two), and muscle spasms (two), as well as cervical pain, backache, swelling joint, MSk discomfort, and polyarthritis (one each). Only one patient had a previous osteoarthritis history (case 29). In 18 patients, gliptin use was considered the only cause of the MSk complaints, whereas in the remaining 16 cases, the information provided was not enough to reject alternative causes. Two patients had a positive re-challenge (cases 10 and 17).

In 26 out of 34 cases, gliptins were considered the only suspected drug (sitagliptin [20], vildagliptin [5] and saxagliptin[1]). Eleven of these 26 patients had used a fixed-dose combination of a gliptin + metformin (sitagliptin [7] and vildagliptin [4]). The latency period ranged from 2 days to 5 months. In 18 out of 26 cases, the MSk complaints improved after gliptin withdrawal.

Seven patients were on long-term treatment with statins, and they received a concomitant prescription of gliptins. The statins were atorvastatin (four patients), simvastatin (two), and pravastatin (one). These seven patients began treatment with sitagliptin (six) and vildagliptin (one); the latency period ranged from 1 to 15 days. In three out of seven cases, the ADR disappeared after gliptin withdrawal (it is unknown whether the statins were withdrawn). In another case (case 34), sitagliptin was prescribed 6 days before rosuvastatin. In this case, the MSk reaction appeared 34 days later, and the patient recovered after only the gliptin was withdrawn.

From March 2007 to May 2012, a total of 58 217 reports were retrieved from the SPvS database. The ROR for the most frequent MSk reactions, myalgia, pain in extremity, and arthralgia, was significantly >1 for gliptins (ROR 1.96 [95% CI 1.12–3.43], $p < 0.025$; 6.88 [95% CI 3.63–13.07], $p < 0.01$; and 2.69 [95% CI 1.38–5.24], $p < 0.05$, respectively), and also when gliptins where compared with other oral antidiabetic drugs in a separate analysis. Moreover, a significant disproportionality was observed when the spontaneous reports with at least one of the most frequent MSk ADRs were considered as cases (ROR 2.97 [95% CI 2.04–4.34]; $p < 0.01$), see Supporting Information.

DISCUSSION

In this study, up to 10.2% of the spontaneous reports involving gliptins described MSk reactions. The most frequent were myalgia, pain in extremity, and arthralgia. A significant association between these ADRs and gliptin use was observed. Although most MSk reactions

Table 1. Detailed information on the 34 spontaneous reports of musculoskeletal adverse reactions with gliptins as the suspected drug

Case	Age/sex	Suspected drug	Adverse drug reactions	Time to onset (days)	Action/outcome
1	71/F	Saxagliptin	Myalgia	30	U/U
2	47/F	Sitagliptin	Arthralgia, joint swelling, joint stiffness	3	W/R
3	71/F	Sitagliptin	Pain in extremity, arthralgia	7	W/R
4	56/F	Sitagliptin	Myalgia	<1	W/R
5	70/F	Sitagliptin	Muscle weakness	30	W/R
6	73/F	Sitagliptin	Pain in extremity		U/NR
7	59/M	Sitagliptin	Myalgia, musculoskeletal discomfort	150	W/R
8	81/F	Sitagliptin	Muscle weakness	<1	W/R
9	77/F	Sitagliptin	Muscle weakness, pain in extremity	30	W/R
10	- /F	Sitagliptin	Arthralgia	4	W/R
11	71/F	Sitagliptin	Arthralgia	2	U/U
12	45/F	Sitagliptin	Arthralgia, myalgia	10	W/R
13	62/F	Sitagliptin	Myalgia		U/U
14	71/M	Sitagliptin	Myalgia	150	U/R
15	75/F	Vildagliptin	Myalgia	<1	W/R
16	70/F	Sitagliptin/metformin	Pain in extremity	150	C/NR
17	65/F	Sitagliptin/metformin	Muscle spasms	180	W/R
18	70/M	Sitagliptin/metformin	Pain in extremity	<1	W/R
19	52/M	Sitagliptin/metformin	Myalgia	18	U/U
20	71/F	Sitagliptin/metformin	Myalgia, muscle spasms	3	W/R
21	64/M	Sitagliptin/metformin	Myalgia	20	U/U
22	54/M	Sitagliptin/metformin	Pain in extremity	6	W/R
23	70/M	Vildagliptin/metformin	Arthralgia	30	W/R
24	77/M	Vildagliptin/metformin	Cervical pain	<1	W/R
25	44/F	Vildagliptin/metformin	Myalgia	<1	W/R
26	45/M	Vildagliptin/metformin	Polyarthritis	30	U/R
27	76/F	Sitagliptin Atorvastatin	Pain in extremity	1	W/R
28	79/F	Sitagliptin Atorvastatin	Arthralgia	2	W/R
29	61/M	Sitagliptin Pravastatin	Arthralgia, joint stiffness, myalgia		U/U
30	75/F	Sitagliptin Simvastatin	Arthralgia, myalgia	10	U/NR
31	73/F	 Atorvastatin	Backache, muscle weakness	1	W/R
32	73/F	Sitagliptin/metformin Simvastatin	Pain in extremity	5	C/IR
33	51/M	Vildagliptin/metformin Atorvastatin	Pain in extremity	15	U/U
34	50/M	Sitagliptin* Rosuvastatin	Pain in extremity	40	W/IR

M = male; F = female; U = unknown; W = withdrawn; C = continued; R = resolved; NR = not resolved; IR = in recovery.
*Sitagliptin was prescribed before rosuvastatin.

were mild, these ADRs prompted gliptin withdrawal in almost two-thirds of the reports (22/34 patients). This evidence suggests that MSk discomfort may limit treatment in some patients with possible negative consequences for diabetes management.

Since August 2011, the summary of product characteristics of sitagliptin in Europe includes MSk disorders detected through postmarketing surveillance, and the United States Summary of Product Characteristics also mentions these MSk reactions in its latest update.[8,9] In 2011, the Dutch Pharmacovigilance System published a report with 12 cases of MSk complaints related to sitagliptin use.[10] Recently, five cases of MSk reactions with gliptins have been published: three cases described rhabdomyolysis with sitagliptin and concomitant use of statins and two cases with synovitis following the use of sitagliptin and vildagliptin (one patient each).[3–6]

The underlying mechanism for these ADRs could be explained by the wide distribution of DPP4 in striated muscle. Some studies have shown a reduced amount of CD26, a glycoprotein with DPP4 enzymatic activity in arthritis, osteoarthritis, and chronic fatigue.[11–13] DPP4 inhibition also increases the levels of P substance (thus decreasing the pain threshold) and slightly increases endomorphin-2 levels.[14] It might suggest that gliptins lead to MSk complaints because of an immune imbalance or through modification of pain susceptibility.

Although one pharmacokinetic study did not find any interaction between statins and sitagliptin,[15] in our study, eight patients used concomitantly gliptins and statins. Despite the small sample size, in these cases, we found

a shorter latency time compared with those using gliptins alone. Despite the impossibility of analyzing differences in the severity of MSk ADRs, the shorter latency time could be a subject of further investigation because type 2 diabetes and dyslipidemia have a high prevalence, and these complaints could impair treatment adherence.

On the other hand, the causality analysis showed a clear temporal sequence in all cases of the study. Two-thirds of the patients fully recovered after gliptin withdrawal, and alternative causes that led to MSk complaints could be ruled out in 18 cases. Positive re-challenge is a strong causality criterion. It was confirmed in two cases of the present series.

In conclusion, despite some limitations with the spontaneous reporting systems (e.g., underreporting and selective reporting), the series presented herein is useful in highlighting the MSk disorders in patients treated with gliptins. Additionally, the significant association observed in the disproportionality analyses could strengthen these findings. Although the MSk reactions were not serious in most cases, two-thirds of patients discontinued their treatment, a situation with clinical and psychological consequences for a patient with a chronic condition. Furthermore, this series suggests that MSk disorders could appear earlier in patients being treated with statins, a hypothesis that could only be confirmed with a more detailed series of reports. It is important that physicians are aware of the occurrence of MSk complaints in diabetic patients treated with gliptins.

CONFLICTS OF INTEREST

All the authors declare they have no conflict of interest with any of the medicines described in this study.

KEY POINTS

- The MSk discomfort is an adverse reaction that could worsen the adherence treatment in diabetic patients.
- By using a spontaneous reporting system, it is possible to enhance the knowledge of MSk complaints in diabetic patients being treated with gliptins.
- In some cases, concomitant use of gliptins and statins could precipitate MSk adverse reactions, but future observational studies should be performed to confirm this finding.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Supplemental Data. Association between gliptin use and musculoskeletal adverse drug reactions

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Supplemental Data: Association between gliptin use and musculoskeletal adverse drug reactions.

	Cases	**Non-cases**	**All database**	**ROR (95% CI)**	***P***
Myalgia	13/1190	319/57 027	58 217	1.96 (1.12-3.43)	<0.025
Pain in extremity	10/270	322/57 957	58 217	6.88 (3.63-13.07)	<0.001
Arthralgia	9/603	323/57 614	58 217	2.69 (1.38-5.24)	<0.005
At least one of most frequent MSk ADRs	30/1902	302/56 315	58 217	2.97 (2.04-4.34)	<0.001

	Cases	**Non-cases**	**Other oral Antidiabetic drugs***	**ROR 95% CI**	***P***
Myalgia	13/40	319/2 270	2 310	2.94 (1.50-5.77)	<0.01
Pain in extremity	10/16	322/2 294	2 310	10.21 (3.68-28.28)	<0.001
Arthralgia	9/23	323/2 287	2 310	3.91 (1.68-9.11)	<0.001
At least one of most frequent MSk ADRs	30/73	302/2 237	2 310	4.47 (2.76-7.24)	<0.001
* The gliptins were compared to the reports describing other oral antidiabetic as the suspected drugs.					

4.2 Dronedarone and renal impairment: evaluation of Spanish postmarketing reports and review of literature.

Tarapués M, Cereza G, Figueras A.

Expert Opin Drug Saf. 2015 Jun;14(6):807-13

Original Research

EXPERT OPINION

Dronedarone and renal impairment: evaluation of Spanish postmarketing reports and review of literature

Mónica Tarapués†, Gloria Cereza & Albert Figueras
Universitat Autònoma de Barcelona, Pharmacology, Therapeutics and Toxicology Department, Barcelona, Spain

Background: Renal impairment associated with dronedarone use is hardly known. Our aim is to describe the characteristics of spontaneous reports involving renal adverse reactions with use of dronedarone.
Methods: In the Spanish Pharmacovigilance database, reports with renal reactions and dronedarone until May 2014 were retrieved and analyzed. Also, a review of case reports of renal failure and dronedarone was conducted in MEDLINE.
Results: Dronedarone was found as a suspected drug in 192 reports, 10 (5.2%) of these reports described renal reactions. Renal reactions appeared until 3 months after the onset of dronedarone treatment. In 5 out of 10 cases, dronedarone was withdrawn and the patient recovered. The Reporting Odds Ratio was 2.88 [95% CI 1.52 – 5.46; $p < 0.05$]. Additionally, eight cases were found in the medical literature. In five of them, the patient outcome was described as recovered. One patient had to undergo hemodialysis for the treatment of their renal impairment.
Conclusions: The effect of dronedarone on the renal function is supported by limited information; therefore, the cases from spontaneous reporting system and those from the medical literature could give relevant additional information. Our analysis shows a potential relationship between dronedarone use and renal impairment. Further studies are needed to confirm these findings.

Keywords: atrial fibrillation, dronedarone, pharmacovigilance, renal failure

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1. Introduction

Dronedarone is an antiarrhythmic drug approved in the European Union and the United States (US) for the treatment of paroxysmal or persistent atrial fibrillation and therapy after cardioversion in patients with atrial fibrillation or flutter in 2009. It is a multichannel blocker non-iodinated derivate of amiodarone; its action mechanism meets the criteria of all Vaughan Williams antiarrhythmic drug classes: inhibition of the rapid Na^+ current (class I), the α and β adrenergic receptors (class II), as well as K^+ currents (class III) and blockade of slow Ca^{2+} currents (class IV). Dronedarone was launched as a safer option than amiodarone, especially due to its apparent lack of skin, lung and thyroid toxicity. A better tolerability is suggested because dronedarone has a short plasma half-life and less lipophilic attribute; it would thus reduce organ toxicity [1,2].

Despite the novel chemical advantages of dronedarone, some safety problems have turned up. Early in 2011, the European Medicines Agency (EMA) and the FDA released a safety alert following the reports of severe liver injury. Later in the same year, the manufacturer announced the discontinuation of PALLAS study

because of the occurrence of severe cardiovascular events in some patients taking dronedarone [3]. Therefore, the FDA as well as the EMA recommended that dronedarone should be restricted to patients with paroxysmal or persistent atrial fibrillation once sinus rhythm has been obtained and it should not be used in patients with unstable hemodynamic conditions especially those with permanent atrial fibrillation, current heart failure or left ventricular systolic dysfunction [4,5].

Regarding dronedarone and kidney function, severe renal impairment is a contraindication for dronedarone use and a periodical monitoring of blood creatinine levels is recommended. In the latest update of Summary of Product Characteristics (SPC) in the US acute renal failure was included as an adverse reaction, but in Europe only small increases in blood creatinine levels (mean 0.11 mg/dl or 10 umol/l) are mentioned [2,6]. Despite the recommendations of renal monitoring, a revision of the two clinical databases in the US estimated that only 50% of patients receiving dronedarone underwent periodical renal tests [7].

Renal impairment is a clinical condition often associated with underlying comorbidities such as diabetes, cardiac failure, ischemic heart disease or hypertension. In the US, it estimated a rising of incidence from 323 to 522 per 100,000 population between 1996 and 2003 [8]. Drug-induced renal impairment is a relevant concern especially with use of cardiovascular drugs such as diuretics, angiotensin II-converting enzyme inhibitors and angiotensin II-receptor blockers [9]. In Spain, a recent study showed that renal adverse effects were the most common adverse drug reactions (ADRs) that lead to hospital admission [10].

Information regarding dronedarone use and renal function is scarce; a pharmacokinetic study in healthy subjects showed that dronedarone reduces creatinine clearance by inhibition of tubular organic cation transporters, although this inhibition was not correlated with a decline in the glomerular filtration rate [11]. Thus, the risk of renal impairment associated with dronedarone use in clinical practice remains unclear. Spontaneous reporting is an effective pharmacovigilance method to increase the safety profile knowledge of new drugs in clinical settings, especially during the first postmarketing years. The aim of the present study is to analyze the clinical information supporting the association between dronedarone use and renal impairment using the Spanish Pharmacovigilance System Database and also to review the case reports in the literature.

2. Methods

2.1 Spanish pharmacovigilance system database

The Spanish pharmacovigilance system (SPvS) was created in 1984 and consists of a network of 17 regional centers. Since then, it has received > 196,000 spontaneous reports of ADRs from healthcare professionals and pharmaceutical industries. Each report is carefully analyzed and included in a specific database. All ADRs reported are codified using the Medical Dictionary of Regulatory Activities (MedDRA®).

In the SPvS database, all spontaneous reports involving dronedarone as a suspected drug as the date it was marked in Spain until May 2014 were retrieved and analyzed. A standardized MedDRA® query (SMQ) was used to identify renal-ADRs reports [12]. SMQ are groups of MedDRA® terms in relation with a defined medical condition. In this study a narrow SMQ for acute renal failure was used, by default this SMQ excluded terms in relation with investigational findings such as increased blood creatinine levels and electrolyte imbalances. The following terms were included: "acute phosphate nephropathy", "acute prerenal failure", "anuria", "azotemia", "continuous hemodiafiltration", "dialysis", "hemodialysis", "nephropathy toxic", "oliguria", "peritoneal dialysis", "prerenal failure", "renal failure", "renal failure acute" and "renal impairment".

In order to strengthen the evaluation of a potential association between dronedarone and renal impairment the case/non-case method was applied in the database and the reporting odds ratio (ROR) was used as the disproportionality measure [13]. All the spontaneous reports identified through the query for acute renal failure in the database were considered as cases and the remaining reports with other ADRs were non-cases. The ratio cases/non-cases with dronedarone use was compared with the ratio cases/non-cases for all other drugs. For an ROR to be considered as significant, the minimum criteria were: ROR confidence intervals 95% > 1 and three or more cases reported. Also, a sensitivity analysis was made comparing the ratio cases/non-cases observed with dronedarone faced to amiodarone, its chemical ancestor. The analyses were conducted using the SPSS 19.0 statistical software.

2.2 Literature review

A MEDLINE search was conducted to identify all case reports with renal-ADRs and use of dronedarone published until May 31st 2014. The Medical Subject Heading term "dronedarone" was combined with "acute kidney injury" or "renal insufficiency". The search was restricted to human studies. There was no language restriction. Only original case reports or case series were included.

3. Results

3.1 SPvS database

Dronedarone was found as suspected drug in 192 cases included in the SPvS database, during the study period. Up to 10 cases (5.2%) described the following renal-ADRs: renal failure (5 cases), acute renal failure (4), and renal impairment (1) (**Table 1**).

The median age of the sample reports (six women and four men) was 70.6 years (range 56 – 85). In nine reports the ADRs were considered as serious; in fact, one patient died and in other seven patients ADRs lead to patient hospitalization. The range of time to onset was between 1 and 118 days (mean 29.6 days). Two of these 10 patients suffered from

Table 1. Characteristics of patients using dronedarone with renal adverse drug reactions reported to the Spanish pharmacovigilance system.

Patient age/ gender	Relevant medical history	Suspected drugs	Time to onset ADRs (days)	Adverse drug reactions	Concomitant drugs	Action/out-come (days to recovery)
70/F	–	Dronedarone	1	Renal failure	Telmisartan, bisoprolol, doxasozin, bromazepam, acenocoumarol	W/–
56/M	–	Dronedarone	5	Acute renal failure (4.8 mg/dl)	ACEI, β blockers, omeprazol	W/–
77/M	–	Dronedarone	± 60	Renal impairment	–	W/R (-)
67/M	–	Dronedarone	41	Renal failure (1.56 mg/dl)	–	–/–
70/F	HF normal LVF, Pulmonary oedema, HT, DM	Dronedarone	23	Renal failure, worsening HF, acute hepatitis, multiple organ failure	Furosemide, acetylsalicylic acid, rosuvastatin, bisoprolol, acenocumarol	W/IR
80/F	HT, dyslipidemia, PVD	Dronedarone	118	Renal failure (1.38 mg/ dl), liver failure	Olmesartan/hydroclorothia-zide, acenocumarol, clorazepate	W/D
52/F	Kidney transplant recipient	Dronedarone Tacrolimus	8 3 years	Renal failure (3.88 mg/ dl), pharmacological interaction	Rivaroxaban	W/R (-)
85/F	Hypertensive benign cardiomy-opathy, previous MI	Dronedarone Eplerenone Atorvastatin	15 1 4 years	Acute renal failure (3.53 mg/dl), liver necrosis	Furosemide, omeprazol, bisoprolol, acenocoumarol, methylprednisolone	W/R (7)
64/M	CRF	Dronedarone Ranolazine	18 4	Acute renal failure (2.7 mg/dl), atrioventricular block	Irbesartan, atenolol, rosuvastatin, acenocoumarol	W/R (11)
85/F	CRF, HF, VHD	Dronedarone	± 7	Acute renal failure (3.7 mg/dl), hepatitis, diarrhoea, vomiting	Cardesartan, furosemide, bisoprolol, acenocoumarol, bromazepam, acetilcoline	W/R (-)

–: No information; ACEI: Angiotensin II-converting enzyme inhibitors; CRF: Chronic renal failure; D: Death; DM: Diabetes mellitus; F: Female; HF: Heart failure; HT: Hypertension; IR: In recovery; LVF: Left ventricular function; M: Male; MI: Myocardial infarction; PVD: Peripheral vascular disease; R: Recovered; VHD: Valvular heart disease; W: Withdrawal.

chronic renal failure (CRF) (Table 1, cases 9 and 10). The blood creatinine level was reported in seven cases; the range of creatinine level in those patients without CRF was 1.38 – 4.8 mg/dl (five patients).

Renal-ADRs alone were described in four cases (Table 1, cases 1 to 4). The remaining six cases also presented other ADRs (hepatic [four cases], cardiovascular [2], and gastrointestinal, multiple organ failure and pharmacological interaction [one each]). Six patients were fully (5) or partially (1) recovered after dronedarone withdrawal. The final outcome for one patient was death. The number of days to recover after dronedarone withdrawal was described in two cases (7 and 11 days). The outcome and the action taken with dronedarone use were unknown in one patient.

Dronedarone was the only suspected drug in seven cases. In the remaining three cases tacrolimus, eplerenone, atorvastatin and ranolazine were described as concomitant suspected drugs. The time elapsed from starting use of dronedarone and the onset renal-ADRs ranged from 1 to 118 days. Furthermore, in 7 out of 10 patients the exposure to the following drugs with known risk for renal dysfunction was observed; angiotensin II-receptor blockers (4), furosemide (3), hydrochlorothiazide (1), and angiotensin II-converting enzyme inhibitors (1), although the starting and ending dates for these drugs were unavailable.

Information related to an underlying disease was described in half of cases. The most common comorbidities were heart failure (two cases), hypertension (2), CRF (2) and recently kidney transplant (1).

Since dronedarone's launching date in Spain (December 2009) until May 2014, a total of 58,400 spontaneous reports were found in the SPvS database. For the ROR calculation, they were considered as cases all the reports with renal-ADRs identified by the use of the query for acute renal failure (n = 1099). The ROR for the association renal-ADRs with dronedarone use showed a statistical disproportionality in the database (ROR 2.88 [95% CI 1.52 – 5.46], $p < 0.05$) (Table 2). In the sensitivity analysis renal-ADRs and dronedarone also showed a significant association when it was compared with amiodarone (ROR 5.20 [95% CI 2.18 – 12.42], $p < 0.05$) (Supplemental data).

Table 2. Reporting odds ratio for association of renal adverse drug reactions and dronedarone.

	Cases	Non-cases	All database	ROR (95% CI)	ROR (95% CI) sensitivity analysis
Renal adverse drug reactions	10/1099	182/57,301	58,400	2.88 (1.52 – 5.46)*	5.20 (2.18 – 12.42)*

*p value < 0.05.
‡Amiodarone was taken as a control drug.

3.2 Literature review

A total of eight case reports of patients with renal-ADRs under treatment with dronedarone were found through a literature review. Six of the eight cases were reported to the Italian pharmacovigilance system [14]. The other two cases were single reports: a case report from the US regarding renal failure associated with worsening heart failure and other one from the UK in relation with a kidney injury requiring hemodialysis [15,16]. These published cases were four males and four women with age ranging 47 – 79 years (Table 3).

Hypertension, diabetes mellitus and cardiac disorders (heart failure, arrhythmia and myocardial infarction) were common underlying disorders described. After starting dronedarone, the time to onset renal-ADRs ranged from 3 – 30 days.

In the six Italian spontaneous reports, other suspected drugs were fenofibrate and olmesartan. Three patients used concomitant drugs associated with renal dysfunction (spironolactone, furosemide and aliskiren). Dronedarone was withdrawn in all cases. In five cases the patient outcome was described as recovered and one patient had to undergo hemodialysis for the treatment of his renal impairment (Table 3, case 8). All of these cases were identified in hospital settings.

4. Discussion

The series of cases of RE-ADRs and dronedarone use reported to the SPvS until May 2014, adds 10 cases to the 8 cases reports already published in the medical literature. Increases of blood creatinine without renal impairment function are known ADRs in patients with atrial fibrillation that received dronedarone. However, information regarding abnormal renal function and dronedarone use is limited; therefore the findings presented here could add some relevant information to take into account in clinical practice.

At present, up to 18 cases of patients experiencing renal-ADRs after starting dronedarone use have been found (10 cases from the SPvS and 8 published in the medical literature). These cases described acute renal failure (10), renal failure (7 patients), and renal impairment (1). Six of the already published cases were part of a review in the Italian spontaneous reporting system in 2013 [14]. It is important to highlight that in 16 patients these ADRs lead to hospitalization or prolonged the hospitalization. A coherent temporal sequence between the dronedarone exposure and renal-ADRs was observed in all cases. Also, in most cases (16/18) these ADRs appeared during the first month of treatment, and therefore it could suggest that renal-ADRs are likely associated with recently dronedarone starting treatment. Additionally, clinical recovery after dronedarone withdrawal was observed in 11 patients (positive dechallenge).

Underlying illnesses were described in 11 of these 18 patients (six SPvS cases, five published cases). Some of these illnesses may predispose to the appearance of renal impairment such as cardiac disorders, hypertension or diabetes. Atrial fibrillation and heart failure are comorbidities, which usually coexist and each condition predisposes to the other. Renal impairment is frequent among patients with cardiac diseases [8]. In the present case series, underlying illnesses could be considered as confounders in the causality assessment of dronedarone, indeed some patients have more than one of these potential confounder factors. Despite this, dronedarone should not be ruled out as a potential pharmacological cause.

However, in half of these patients (10/18) a concomitant use of angiotensin II-converting enzyme inhibitors, angiotensin II-receptor blockers or diuretics was reported; it is to be noted that any caution about the concomitant use of these cardiovascular drugs with dronedarone is not mentioned either on the US or the European SPC [2,6]. Our observation might suggest a possible interaction between dronedarone and drugs with potential renal effect. This observation is supported by the short time to the onset of renal-ADRs observed after starting dronedarone in patients with chronic use of other cardiovascular drugs that may affect the renal function. Further observational studies are needed to investigate this finding.

Also, one patient had a fatal outcome (Table 1, case 6). According to the information described in the report, the cause of death was toxic hepatitis and renal failure. This patient was taking olmesartan and hydrochlorothiazide 4 months before the introduction of dronedarone. This observation might also suggest the concern about concomitant use of drug with known renal effect and dronedarone. Also, a possible acute relationship between renal and hepatic dysfunction might impair the drug metabolism and the whole body response.

Regarding the renal function, dronedarone showed about an 18% reduction of creatinine clearance in a pharmacokinetic study carried out among 12 healthy male volunteers. [11]. This clearance reduction is caused by an inhibition of tubular cation transporters; however, in the light of the cases analyzed here, the actual mechanism of renal impairment

Table 3. Characteristics of case report published in the medical literature.

Author (year)	Patient age/gender	Relevant medical history	Suspected drugs	Time to onset ADRs (days)	Adverse drug reactions	Other drugs described	Action/outcome (days to recovery)
Coons *et al.* (2010) [15]	47/M	Non-ischemic cardiomyopathy, ejection fraction 15 – 20%, HF, MVT, PH	Dronedarone	3	Acute renal failure, worsening heart failure, hepatic failure	Furosemide, spironolactone, ramipril	W/IR
Biagi *et al.* (2013) [14]	76/F	DM, HT, hyperthyroidism, myocardial infarction	Dronedarone Fenofibrate	6 8	Renal failure	Aliskiren, furosemide, furosemide/spironolactone, atenolol, glibenclamide/metformin, enoxaparin, sodium, levothyroxine	W/R (13)
Biagi *et al.* (2013) [14]	76/F		Dronedarone	6	Acute renal failure, asthenia, nausea, tremor, vomiting	Digoxin	W/R (-)
Biagi *et al.* (2013) [14]	79/M	Septic shock, pulmonary fibrosis, hypothyroidism	Dronedarone	8	Acute renal failure, secondary anaemia	Enalapril, spironolactone, furosemide, allopurinol, potassium, salmeterol/fluticasone, levothyroxine, warfarin, clonidine, tiotropium bromide, oxygen	W/R (-)
Biagi *et al.* (2013) [14]	61/F		Dronedarone	13	Acute renal failure, acute renal tubular necrosis, bradycardia	Pantoprazol, indobufen, beclomethasone, dipoprionate/formoterol, tiotropium bromide, atorvastatin, levosulpiride	W/(-)
Biagi *et al.* (2013) [14]	73/F		Dronedarone	6	Renal failure		W/R (8)
Biagi *et al.* (2013) [14]	73/M	Rectal adenocarcinoma, dehydration, rectal resection, ileostomy	Dronedarone Olmesartan	30 120	Acute renal failure	Esomeprazol, enoxaparin, levothyroxine	W/(-)
Young *et al.* (2013) [16]	72/M	HT, DM, hypercholesterolemia, gout, coronary artery bypass	Dronedarone Bisoprolol	5 12	Acute renal failure	Digoxin, atorvastatin	W/R (-)

-: No information; DM: Diabetes mellitus; F: Female; HF: Heart failure; HT: Hypertension; M: Male; IR: In recovery; MVT: Monomorphic ventricular tachycardia; PH: Pulmonary hypertension; R: Recovered; W: Withdrawal.

remains unknown. Moreover, it is important to bear in mind that in the ANDROMEDA study an increase of blood creatinine was already observed in 2.6% of patients in the dronedarone group compared with none in the placebo group (2.6 and 0%; respectively $p < 0.01$). It had also been mentioned that dronedarone might interfere with renal clearance of other cardiovascular drugs [17]. In addition, in the ATHENA study the increase in blood creatinine was classified as an event deserving medical treatment, and it was more frequent observed in the dronedarone group (108 patients [4.7%] and 31 [1%]) $p < 0.001$) [18]. Furthermore, in 2010 two independent safety reports analyzed the relationship between renal impairment and dronedarone, the Uppsala Monitoring Centre-Collaborating Centre of World Health Organization (14 reports worldwide) and later, the Institute for Safe Medication Practices (15 reports in US) [19,20].

The present study has some limitations inherent to the spontaneous reporting methodology, for instance underreporting and incomplete information are the most important concerns to deal with. However, a significant ROR of 2.88 [95% CI 1.52 – 5.46; $p < 0.05$] strengthened the association between dronedarone use and renal impairment in the SPvS database. Also, this disproportionality measure was still observed when only spontaneous reports with dronedarone and amiodarone were compared (ROR 5.20 [95% CI 2.18 – 12.42], $p < 0.05$). In our opinion this study, despite its limitations, could give an overall sight of renal disturbances reported with dronedarone use in clinical settings.

5. Conclusion

The information about the safety profile of new drugs is the result of a construction process; hence, the safety of dronedarone is being built up yet. Despite the limitations described, spontaneous reporting is a good tool that allows us to greatly improve the knowledge about the safety profile of the new drugs in postmarketing surveillance. The potential role of dronedarone on the renal function is based on limited information, and taking into account that patients with atrial fibrillation are high-risk population, the cases gathered in this study could add some additional information for clinicians and researchers. More spontaneous reports sent from clinical practice, as well as further observational studies, could enrich and improve our knowledge about this safety issue. In the meantime, monitoring of renal function is highly recommended with dronedarone use, especially in those patients with several comorbidities and in those ones on treatment with other drugs which may affect kidney function.

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Affiliation

Mónica Tarapués[1,2] MD, Gloria Cereza[1,2,3] MD & Albert Figueras[1,2] MD
[†]Author for correspondence
[1]Pharmacology, Therapeutics and Toxicology Department, Universitat Autònoma de Barcelona, E-08193 Bellaterra (Cerdanyola del Vallès), Barcelona, Spain
E-mail: mtr@icf.uab.cat
[2]Fundació Institut Català de Farmacologia, E-08035 Barcelona, Spain
[3]Catalan Centre of Pharmacovigilance, Spanish Pharmacovigilance System

Supplementary materials available online

Supplemental data

SUPPLEMENTAL DATA

Table 1. Contingency table for Reporting odds Ratio Calculation.

	RE-ADRs	**Other ADRs**
Reports with Dronedarone	10	182
Reports with other drugs	1089	57,119
ROR (95% Confidence Intervals)	2.88 (1.52 – 5.46)*	

* *p<0.05*

Table 2. Contingency table for Sensitivity analysis.

	RE-ADRs	**Other ADRs**
Reports with Dronedarone	10	182
Reports with Amiodarone*	11	1041
ROR (95% Confidence Intervals)	5.20 (2.18 – 12.42)**	

* *Amiodarone was taken as a control drug . ***p<0.05*

5. General discussion

The studies carried out in the context of the present thesis have contributed to the knowledge of the safety profile of new medicines for the treatment of CVD. So, the results provided useful information regarding: (i) the suspicion of musculoskeletal complaints associated with the use of gliptins (sitagliptin, vildagliptin, saxagliptin), an ADR that has been recently alerted by the FDA (47); (ii) the potential risk of renal impairment and ventricular arrhythmia associated with dronedarone use, and (iii) additional safety information regarding ranolazine and rosuvastatin was also found.

5.1 New safety information of medicines for treatment of chronic diseases

Different areas have been covered in the present work such as new approaches for the treatment of type 2 diabetes mellitus, atrial fibrillation, angina and hypercholesterolemia.

5.1.1 Type 2 Diabetes Mellitus

The main objective of the management of Type 2 Diabetes Mellitus (T2DM) consists in controlling the glucose blood levels and the acute complications; notwithstanding this, the most important long-term therapeutic goals are related to control of microvascular complications including retinopathy, nephropathy and neuropathy, and macrovascular complications such as cerebral, coronary and peripheral artery disease. Metformin has being the unique antidiabetic drug evaluated for decreasing long-term cardiovascular complications (48). New therapeutic options in T2DM have showed efficacy to reduce the glycated haemoglobin A1C (HbA1c). Specifically, DPP-4 inhibitors have demonstrated efficacy in reducing and controlling the levels of HbA1c, although their contribution for controlling the cardiovascular morbidity/morbidity is unclear.

In Spain, the regulatory agency has approved sitagliptin, vildagliptin and saxagliptin in monotherapy, dual therapy and in combination for triple therapy. Also, the current guidelines for managing T2DM have accepted the use of these new antidiabetic medicines as an effective pharmacological strategy (7).

In study I, it was analysed the potential association of DPP4-inhibitors use with musculoskeletal (MSK) complaints such as arthralgia, myalgia and pain in extremity mainly. These ADRs, regardless

of not being considered as clinically serious, could significantly impair the quality of life of the affected patients, and even be the cause of treatment discontinuation a situation that might affect the therapeutic goals of the treatment of T2DM.

This study also suggested a potential relationship between the concomitant use of DPP-4 and statins with the occurrence of MSK reactions. So, MSK complaints might decrease the adherence to diabetes treatment, and it seems that DPP-4 inhibitors could intensify the well-known muscular pain associated with statin treatment (49). This represents an interesting hypothesis, especially because T2DM and dyslipidemia are usual comorbidities that affect some patients simultaneously and, both are serious risk factors for CVD.

It should be highlighted that, after this publication other musculoskeletal complains with gliptin treatment have turned up, especially arthritis (50–52). Recently, in a review of its database, the FDA found 33 cases of severe arthralgia with sitagliptin, saxagliptin, linagliptin and alogliptin. In five cases, the patients experienced arthralgia with the treatment of two different gliptins (47). This is an example of the strengthening of the initial hypothesis that deserves a large observational study. Probably, it could be suggested to update gliptins SPC in order to alert about musculoskeletal ADRs.

5.1.2 Atrial Fibrillation

Dronedarone, a new antiarrhythmic drug, was launched as a safer option to amiodarone, especially in those patients with low tolerability to the old medicine. Its therapeutic indication is paroxysmal or persistent atrial fibrillation (AF). In study II, an association between dronedarone use and renal impairment was analysed.

Amiodarone is considered as an effective antiarrhythmic treatment in patients with AF, although its frequent ADRs limit its applicability in clinical practice. Dronedarone is a new amiodarone derivative that seems to show a better safety profile, especially regarding those reactions related to the deposit of the drug, such as skin, pulmonary and thyroid toxicity. However, it is contraindicated in permanent AF and grade III and IV heart failure (53).

Renal failure is an important concern in the context of AF disease, and with remarkable relevance in patients with heart failure. Dronedarone use is contraindicated in patients with severe renal failure; even though the action of dronedarone on renal function is not well defined.

The potential relationship between dronedarone and renal impairment described in study II was strengthened with a review of the published cases. In this case, there are several confounding factors that could reduce the potential association between dronedarone and renal ADRs; notwithstanding, the suspected ADR should not be dismissed.

This study also highlighted potential interactions between dronedarone and concomitant drugs with well-known effect on renal function, such as those patients in treatment with diuretics,

angiotensin II-converting enzyme inhibitors, or angiotensin II-receptor blockers. It is important to bear in mind that patients with AF suffer from other diseases, and renal dysfunction could increase the toxicity of the remaining concomitant treatment.

Another interesting research was the potential association of dronedarone with ventricular arrhythmia. Dronedarone has had serious safety signals, though not one in relation with heart conduction. The pro-arrhythmic effects of dronedarone were analysed in the FDA database (54); however, no other signals had been published. In the WHO international database, a potential relationship between dronedarone and ventricular arrhythmias has turned up in 2014, and this review described 33 cases of ventricular arrhythmia found in the WHO international database (55) [see Appendix 1]. The potential role of dronedarone in the mechanism of arrhythmias remains unknown, but in the ANDROMEDA trial sudden death was more frequent in the dronedarone group (56). Moreover, it is important to remember that patients with atrial fibrillation are at high risk due to several comorbidities, polypharmacy and sometimes other structural heart or conduction disorders. So, this report also contributed to the knowledge of cardiac risk of a new antiarrhythmic drug.

5.1.3 Enhancing the knowledge of other drugs: ranolazine and rosuvastatin

Detailed analysis of spontaneous reports could help to uncover safety problems. Cases retrieved reports from the spontaneous reporting databases still contribute to the knowledge of recently marked medicines. Some other contributions have been also published in the context of the present thesis.

Ranolazine is a new anti-anginal drug approved as a second-line therapy of stable angina. In the periodical revision of the spontaneous reports with this drug, a case of serious long QT interval was found. This case also showed a potential interaction between ranolazine and amiodarone. There is a theoretical QT interval enlargement associated with the use of ranolazine. Furthermore, this new anti-anginal medicine has restrictions regarding its concomitant use with other antiarrhythmic drugs, except to amiodarone, and severe renal failure is a strong contraindication criterion. The described patient (57) [see Appendix 2] had other risk factors such as dyslipidemia, diabetes, hypertension, atrial fibrillation, heart failure, and severe chronic renal failure, which could be considered as confounders. Notwithstanding this, the association of ranolazine with QT interval enlargement and a potential interaction with amiodarone should not be excluded. This information also contributed to the knowledge of ranolazine, and to increase the awareness of clinicians regarding these events in their clinical practice.

The last contribution was the finding of fatigue reported in patients treated with rosuvastatin. The association of statins with muscular pain and in the worst cases with rhabdomyolysis is well known. Recently, a RCT analysed fatigue and less energy associated with atorvastatin and pravastatin (58). This attracted our attention, and a review of the FEDRA database was carried out looking for fatigue with one of the latest statins, rosuvastatin. This analysis suggested that

fatigue and loss of energy are also reported with rosuvastatin, despite that fatigue as an isolated event was infrequently reported to the pharmacovigilance system. In agreement with the authors of the RCT it was postulated that these ADRs could have a negative effect in patients with dyslipidemia, especially because physical exercise should be part of the non-pharmacological approach advised to these patients (59) [See Appendix 3].

Nowadays, patients are exposed to polypharmacy as a consequence of multimorbidity, and the control of many diseases in one patient is a real challenge for the physicians in clinical practice. Within this framework, the post-marketing surveillance is crucial, and pharmacovigilance research has a role in the knowledge building-up process for new medicines.

5.2 Widening of therapeutic indications and its impact in pharmacovigilance

One of the main goals of pharmacovigilance is to describe unknown ADRs or new information on an already known association. However, the pharmaceutical market has changed over time and pharmacovigilance (spontaneous reporting system) had to adapt to the new challenges.

Adding a new therapeutic indication to a product or widening the current indication is a new manner of being innovative in the pharmaceutical market and it means a variation in the drug lifecycle compared to few years ago. This phenomenon has been observed especially with oncological drugs or biologics, although it is a common practice in all pharmacological groups, included cardiovascular medicines (60,61). In the case of gliptins, either for sitagliptin, vildagliptin or saxagliptin the first therapeutic indication was dual therapy for management of T2DM, and later on monotherapy and triple therapy (62).

An investigation of the current trends of several new chemical entities and in the FAERS could not find any recognizable reporting pattern (63). Traditionally, a peak of spontaneous reports during the first 5 years post-commercialization was observed, this was called the Weber effect (64). However, several investigations have suggested that this effect is not observed nowadays, and postulated that some peaks of reporting could be observed after the first 5 years post-commercialization (65,66). Taking into account the continuous changes in the drug-marketing process and widening of indications of use, it seems that the Weber effect might not be observed for some new medicines. These changes should encourage the pharmacovigilance activities for a continuous surveillance in order to identify new ADRs or other new safety information.

The source of drug information for the physician is the SPC. This is a document addressed to health-care professionals in order to provide useful information about the drug and sometimes it is considered as a real prescription guideline (67). As the safety profile of a new drug is provisional when the drug reaches the market, the SPC should be continuously changing especially in the first post-marketing years. Notwithstanding this, (1) some clinicians are unaware of this, and do not check for updates, and (2) the information contained in the SPC is confusing, and its real

usefulness in clinical practice is unknown due to the clinical practice guidelines, that are more frequently used regardless their well-known conflict of interest (68).

5.3 Risk minimization strategies and patient safety

The risk minimization strategies have been developed as activities to encourage a proactive pharmacovigilance in post-marketing settings by the pharmaceutical industry, though this compulsory procedure has raised serious concerns regarding its usefulness and its impact in terms of public health (69–71).

An evaluation made by Giezen Et al., showed that the information in the post-authorization study protocols in pre-approval stages was partial or limited and could hamper the evaluation at the moment of drug approval (69). Moreover, a recent systematic review found several methodological gaps in the assessment of risk minimization interventions both in the EU and in the US (70).

As an example, in the findings presented herein, renal impairment or renal failure is not described as itself in the risk management plan (RMP) of dronedarone. This risk or potential harm is described as the inappropriate management of the signal of serum creatinine increase, and the main actions to be taken are prescription surveys and cross sectional studies, even though since the launch date of this drug in 2009 until mid-2015 the results of such studies have not been published (72).

Regarding gliptins, each gliptin has different market authorization holders, and consequently each has a different RMP. For sitagliptin the risk of myopathy was found as a potential risk, and routine pharmacovigilance was described as activity, together with safety and warning changes in the SPC (73). In vildagliptin, muscular events with or without statins were described and routine pharmacovigilance is the main risk minimization activity (74). In saxagliptin, there is no mention of musculoskeletal events in the RMP (75). None of the available RMP described arthralgia as a potential concern. Likewise, in the case of dronedarone, until mid-2015, there were no data which helped to elucidate the potential risk of muscular harm with their use.

It should to be noted that an independent observational study to find an association between acute renal failure and the use of dronedarone was carried out in Italy recently. No differences were observed between the characteristics of renal failure in patients in treatment with amiodarone compared with patients on dronedarone. Despite this, the researchers suggested caution with the interpretation of the findings because of the few patients in the dronedarone group, which could be a limitation in the comparative analysis. Also, they recommended to be aware of renal reactions with dronedarone in clinical practice (76).

5.4 The Spontaneous Reporting system, its contribution to the patients' safety -Old problems and new ones solutions

Nowadays, post-marketing surveillance is the result of several complementary methods of study. Spontaneous reporting system is one of the most traditional methods in pharmacovigilance, although it has serious well-known limitations that have prompted to use other data sources and analyses.

Spontaneous reporting has many limitations that should be acknowledge: underreporting, lack of information, unknown drug use factors, and competition bias are the most important (33,77–79).Underreporting is one of the main concerns, it is estimated that <10 % of adverse reactions are reported (34). Another factor that limits the findings in these databases is the lack of knowledge about the denominator exposure. Frequently, the use of pharmacoepidemiological strategies helps to overcome the limitation of spontaneous reporting with the use of consumption databases in order to elucidate or verify any potential signal detection. Other strategies are the linkage of spontaneous reports and consumption or reimbursement databases (80). Thus, many authors suggest that the whole approach of pharmacovigilance should integrate traditional methods as the spontaneous reporting with other new ones in order to overcome limitations.

Different pharmacoepidemiology studies have complemented and strengthened or discarded signals generated from spontaneous reports. In the future, probably more accurate clinical records and automated databases would be enough to calculate exposures and risks without biases, but at present, data mining of databases or electronic medical records are just a helpful method to explore the use of drugs in population. In terms of patient's safety, many cases that end in drug withdrawal have started with case reports or case series, especially in Europe (12,13,81).

Some countries have strengthened pharmacovigilance and the spontaneous reporting by reinforcing the regional centres inside their national networks, such as Italy, Spain and France (82–84). This effort includes a careful causality assessment at individual level of each spontaneous report prior its inclusion in the national database. This assessment has improved the whole process of passive pharmacovigilance and helped greatly signal detection. This assessment is unfeasible in schemes such that of the US.

Another useful strategy in pharmacovigilance is the automated methods for detection of new safety signals. Despite of their continuous and more ubiquitous use, the automated signals generated from disproportional observation in big databases have to be managed with caution due to high rates of false signals (85). Some strategies have been developed in order to decrease this disadvantage, and more complex analyses for improving the automated signal detection are still under study. (86–88) Another important strategy in safety signal generation is the use of meta-analytical techniques applied to RCT. This information allows getting a general overview and comparative analysis of the all RCT regarding a specific medicine. (89–91)

Patients' safety will improve with the interaction among prescribers, regulatory agencies and pharmaceutical industry; this is the ideal balance but hardly ever reached. Regulatory agencies have the responsibility to the generation of independent information; however, nowadays academia also has a crucial role in independent evaluation of drug safety. In Europe, twenty four groups are working on drug utilisation research. Their work has enhanced and collaborated to the knowledge of medicines use and their impact on public health (92). Besides this, manufacturers are increasingly interested in speeding up premarketing stages and penetration of new medicines in the market, a process that is contrary to the slowness of knowledge building.

Knowledge regarding the safety profile of new drugs on the market (in this case cardiovascular medicines) is always under construction while the medicine remains available in the market. So, the right prescription is sometimes a challenge in clinical practice, and a careful risk-benefit assessment is always necessary to ensure the maximum level of patients' safety.

6. Conclusions

1. In this thesis, two safety signals regarding new cardiovascular drugs have been revised. Both ADR's might impact treatment adherence; and could be considered detrimental for the underlying conditions of these patients.

2. Musculoskeletal adverse reactions like myalgia, arthralgia and pain in extremities were associated with the use of gliptins (sitagliptin, vildagliptin and saxagliptin). None observational study has verified this association so far, even though a safety alert regarding arthralgia and gliptins use was released by the FDA very recently.

3. Renal impairment associated with the use of dronedarone is a relevant safety concern among patients with atrial fibrillation and concomitant chronic conditions. This finding was supported by reports of the Spanish pharmacovigilance database and other published case reports in medical literature. Renal impairment could be the consequence of a potential interaction with other drugs that may affect renal function.

4. The association between dronedarone and ventricular arrhythmia found in the WHO international database, despite several confounders, suggests a potential harm of this new antiarrhythmic drug. This safety information should prompt clinicians as well as researchers to be aware of this reaction, and maybe take preventive measures. At the same time, further studies should be designed.

5. The case reports involving ranolazine and rosuvastatin are additional examples of the need for continuous search for new safety signals in pharmacovigilance databases, in order to fulfil the most important goal of spontaneous reporting systems: to contribute to the patients' safety.

6. A detailed analysis of the spontaneous reporting databases still contributes to the never-ending process of knowledge acquisition regarding toxicity profile of new medicines, the necessary counterbalance of the often excessively enthusiasm that involve new products.

7. Notwithstanding this, post-marketing surveillance should be understood as the result of several complementary methods. These methods should also include meta-analysis of published RCT's and complex pharmacoepidemiological studies.

7. Appendixes

7.1 Dronedarone and ventricular arrhythmia

SIGNAL

- No cases with a "likely" or "possible" causa lity assessment
- In 90% of the cases, confounding factors such as relevant medical history and/or rele vant context and/or concomitant treatment(s) known to induce such events were present.

Conclusion

There is no pharmacological data or toxicological data in favour of deleterious actions of agomelatine on platelet functions. Additionally, no safety concern regarding "Thrombocytopenia" was raised with agomelatine from clinical data or post-marketing surveillance

Thus the signal "Thrombocytopenia" was refuted and closed. This event will remain under close monitoring.

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Dronedarone and ventricular arrhythmia

Dr. Mónica Tarapués, Ecuador/Spain

Summary

Dronedarone is a new antiarrhythmic drug indicated for the treatment of persistent or paroxysmal atrial fibrillation as well as for restoring the normal sinus rhythm after cardioversion. Alteration to cardiac rhythm is not mentioned as an expected adverse reaction either in the EMA or the US FDA summary of product characteristics. In the WHO Global Database, VigiBase®, there are, as of May 2014, four cases of ventricular arrhythmia in association with dronedarone use. This finding led to an in-depth search and 29 cases of ventricular fibrillation with dronedarone use were also found in VigiBase®. The total of 33 ICSRs were submitted from the United States, Germany and Canada. Some cases have potential risk factors for ventricular arrhythmia. Despite potential confounders 10 patients recovered fully or partially after dronedarone withdrawal. As a multichannel drug, dronedarone has a possible mechanism of action that could explain these serious cardiac events, and this observation together with some consistent reports points to a signal.

Introduction

Dronedarone is a non-iodinated and shorter-acting derivate of amiodarone. It was registered by the US FDA and the EMA in 2009. Dronedarone is indicated for the treatment of paroxysmal or persistent atrial fibrillation in clinically stable patients and for the maintenance of sinus rhythm after successful cardioversion in adults.[1]

Dronedarone is a multichannel blocker that meets the criteria of all Vaughan Williams antiarrhythmic drug classes: inhibition of the rapid Na^+ current (class I), α and β adrenergic receptor inhibition (class II), inhibiting of K^+ currents (class III) and blocking of slow Ca^{2+} currents (class IV). It was launched as a safer option than amiodarone, especially due to its apparent lack of toxicity in skin, lungs and thyroid. A better tolerability is suggested because dronedarone has a less lipophilic characteristic, thus a short plasma half-life is the main feature that would reduce the organ toxicity.[1]

In the summary of the product characteristics of dronedarone, the most common adverse reactions (experienced by at least 10% of the patients) include gastrointestinal disorders such as diarrhoea, nausea, vomiting, abdominal pain and dysgeusia, cardiac disorders such as congestive heart failure and bradycardia, skin disorders such as rashes and pruritus, general disorders such as fatigue and asthenia, and liver function test abnormalities.

The term "ventricular arrhythmia" incorporates a wide spectrum of abnormal cardiac rhythms, such as: premature ventricular complex, sustained monomorphic ventricular tachycardia, polymorphic

ventricular tachycardia, and ventricular fibrillation. Ventricular arrhythmias can occur in individuals with or without cardiac disorders. Monomorphic ventricular tachycardia could lead to sudden cardiac death if it degenerates into polymorphic ventricular tachycardia or ventricular fibrillation. These arrhythmias have a great deal of overlap between clinical presentations and severity. Ventricular arrhythmias occur predominantly in patients with structural heart disease and ischemic cardiac disease, although it can occur in patients with congenital cardiac disorders (associated with surgical scar), electrolyte imbalances and inherited or acquired channelopathies.[2]

Statistical disproportional reporting has been observed in the WHO Global ICSRs Database, VigiBase® for ventricular arrhythmia associated with dronedarone treatment.

Reports in VigiBase®

As of 19 May 2014, there were four ICSRs in VigiBase® that described ventricular arrhythmia associated with dronedarone use. In addition there were 29 ICSRs of ventricular fibrillation, 89 cases of ventricular tachycardia and 62 of cardiac arrest.

The four cases reported with ventricular arrhythmia were submitted from two countries: Germany (three cases) and United States (one case); all the cases were sent by physicians. These ICSRs involved three men and one woman. In one case the patient was described as an adult, and in the other cases the patients were >70 years old. Sudden death and ventricular tachycardia were found as co-reported terms. The four cases are described in Table 1.

Regarding outcome, "recovered" was reported in two patients. In another case the outcome was reported as "unknown", and in the last one outcome was reported as "died". Information regarding other potential risk factors such as baseline conditions, electrolyte abnormalities or cardiac disorders was lacking. Dronedarone was the only suspected drug in all the cases. The time to onset was available in only two cases (17 and 21 days). Causality was assessed as possible in three cases, and unknown in one case. Other drugs with potential cardiac effect were reported as concomitant; ramipril, flecainide, tamsulosin and β-blockers. Neither start nor end dates of these drugs was available.

Additionally, 29 ICSRs with dronedarone and ventricular fibrillation were found in VigiBase®. These 29 reports came from the United States (23 cases), Germany (five cases) and Canada (one case). Twenty seven ICSRs were reported by health-care professionals (physician [17], pharmacist [6] and other health professional [4]); the remaining two ICSRs were reported from consumers. The 29 cases are described in Table 2.

Age was reported in 26 out of 29 ICSRs and ranged from 25 to 88 years with a median age of 68 years. Gender distribution was 19 men and 9 women, and the gender was unknown in one report. In 13 cases the outcome reported was recovered or recovering. Nine of the 13 reports described a drug withdrawn (positive dechallenge), while in four reports it was not clear if the patient recovered before or after the drug was withdrawn. In five patients outcome unknown was reported, and in one case no effect was observed with drug withdrawn.

Eight ICSRs described ventricular fibrillation as a unique cardiac adverse drug reaction. Ventricular tachycardia, torsade de pointes or cardiac arrest were described as co-reported terms in 14 other cases, as well QT interval prolongation in three cases.

In 21 ICSRs relevant medical information was available. The most frequent co-morbidities identified were heart failure (9 cases), cardiomyopathy (11), coronary artery disease (3), hypertension (6), type 2 diabetes mellitus (4) and chronic kidney disease (4). In eight patients abnormal heart rhythms were found (tachyarrhythmia, tachycardia-bradycardia syndrome, or premature ventricular contractions). In addition, nine patients were pacemaker or implantable cardioverter defibrillator users.

In 22 ICSRs dronedarone was the only suspected drug. Time to onset was available in 22 cases; it ranged from the same day the drug was started to 446 days, with a mean value of 81days. In seven cases the dronedarone use was off-label. Other suspected drugs were; amiodarone, metoprolol, levofloxacin, amoxicillin, mexiletine, theophylline, ethanol and quetiapine (one case each). Concomitant drugs with potential cardiac risk such as β-blockers were reported in 12 cases (metoprolol [7], carvedilol [2], bisoprolol [2], atenolol [1]), calcium antagonists in four cases (diltiazem [3] non specific [1]) and digitalis derivates in five cases. Causality was assessed as possibly related to dronedarone in four cases, unknown in 24 cases and unclassified in one case.

Literature and Labelling

Dronedarone is considered a second line treatment; it should only be prescribed after non-response of alternative treatment options. Ventricular arrhythmia or arrhythmia is not mentioned in either the EMA or the US SPCs of dronedarone. Regarding cardiac adverse drug reactions, congestive heart failure and bradycardia are described, as well as QTc Bazett prolonged (>450 msec in male, >470 msec in female). In the warning and precautions section, it is mentioned

that proarrhythmic effects may occur in particular situations such as concomitant use with medicinal products that favour arrhythmia and/or electrolytic disorders. Furthermore, potential interactions between dronedarone and other proarrhythmic drugs are mentioned, especially with β-blocker drugs, calcium antagonists and digoxin.

A restricted use of dronedarone is strongly recommended; especially, dronedarone should not be prescribed in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart). Its use is also contraindicated in patients with second- or third-degree complete bundle branch block, sinus node dysfunction and atrial conduction defects.[1]

In patients treated with amiodarone, bradycardia is the most common cardiac event. However amiodarone has been associated (less frequently) with arrhythmias, conduction disturbances and cardiac arrest events. Dronedarone as antiarrhythmic drug class III and derivate of amiodarone, might have some proarrhythmic action. There is evidence that the inhibition of potassium currents appears to trigger early after depolarizations (EAD) in animals. These EADs may trigger another action potential and promote triggered activity; therefore it might induce reentry and lead to proarrhythmic events.[3,4]

The ANDROMEDA trial was early stopped early due to a high mortality rate (25 patients in the dronedarone group vs. 12 in the placebo group [HR 2.13: 95%CI 1.07-4.25; p=0.03). In this trial, most deaths were due to worsening of heart failure, however deaths due to dysrhythmia or sudden death were also observed in the dronedarone group. It was difficult to draw definitive conclusions regarding cardiac safety of dronedarone because of the presence of potential confounding factors such as severe heart failure and left ventricular systolic dysfunction. Later, in the ATHENA study, the most successful and largest trial, there was no difference in death from any cause in both groups.[4]

Moreover, in 2012 the proarrhythmic potential of dronedarone was analyzed in a review of the FDA adverse event reporting system (FAERS) database. In this study, several reports with ventricular arrhythmias or cardiac arrest, as well as torsade de pointes were found.[5] The authors concluded that further investigation regarding this issue is necessary.[6]

Discussion and Conclusion

In our assessment, four cases of ventricular arrhythmia and 29 cases of ventricular fibrillation were found, a total of 33 cases. Potential risks factors for ventricular arrhythmia were described in 26 out of 33 cases. It is important to bear in mind that there were patients with more than one risk factor, e.g. four patients had both heart failure and cardiomyopathy. It is possible that some of the patients presented with unstable haemodynamic conditions, which would be a contraindication for dronedarone use. Also, in eight cases the therapeutic indication for dronedarone was an off-label use (ventricular arrhythmia). These findings highlight the potential impact of an inappropriate use of dronedarone.

A potential interaction should be taken into consideration. Dronedarone has a warning for concomitant use of β-blockers, calcium antagonists or digoxin. It is recommended to reduce the dose of these drugs especially for increased risk of toxicity. On the other hand, as the washout period was not enough to eliminate arrhythmic events associated with other antiarrhythmic drugs, a residual effect of amiodarone, sotalol or flecainide could be another explanation.

Even though the association of dronedarone and ventricular arrhythmias did not reach statistical difference [IC value 1.38; IC_{025} -0.36], the association of dronedarone and ventricular fibrillation caught our attention due to its statistically significant IC value [IC 3.10; IC_{025} 2.53], thus these combinations stand out against the background of the database. Altogether33 ICSRs showed a plausible temporal sequence.

In 24 ICSRs, information regarding time to onset was available, and extending up to 446 days, but it is important to mention that time to onset in 16 out of the 24 ICSRs that has this information recorded was 2,5 months or less. In addition, in eleven patients a full or partial recovery was observed after dronedarone withdrawal (positive dechallenges). Moreover in two cases (case 2, table 1 and case 17, table 2) dronedarone was not immediately stopped when the events of ventricular arrhythmia and ventricular fibrillation occurred and the patients developed the same events again while still on the medication. When the drug was removed, the patients both recovered.

Some of the potential risk factors described in the ICSRs by themselves could contribute to the occurrence of ventricular arrhythmia; nevertheless the inadequate use of dronedarone together with some cardiac risk factors could increase the proarrhythmic risk, and finally the occurrence of serious ventricular arrhythmias.

Also, in a few patients QT interval prolongation was co-reported. This is a known adverse reaction of dronedarone, but it is important to highlight that persistent QT prolongation could lead to torsade de pointes. This serious and sometimes

fatal reaction is already known for other antiarrhythmic drugs, and further studies are necessary in order to elucidate the potential risk of torsade de pointes and dronedarone.

In conclusion, dronedarone, like other antiarrhythmic drugs, might have a potential arrhythmogenic risk. This risk is an inherent characteristic associated with its multichannel activity. Clinicians should be aware of the cardiac adverse reactions observed with its use in clinical practice. We consider ventricular arrhythmias such as ventricular fibrillation in patients taking dronedarone as a signal because as an antiarrhythmic drug its inhibitory action on potassium channels might explain the arrhythmic events. There are also consistent reports of positive dechallenges in VigiBase®. The cardiac baseline condition of the patients and the concomitant medication can act as inevitable confounders, which is to be expected according to the indication for treatment with dronedarone. Further studies are needed to confirm these findings.

Table 1. Characteristics of four reports for dronedarone and ventricular arrhythmia in VigiBase®

Case	Age/ Sex	Medical history	Suspected (S) and conco- mitant (C) drugs	Time to onset	Indication	Action Drug	ADR terms (WHO-ART)	Outcome
1	Adult/M	Implanted cardioverter defibrillator user	Dronedarone (S) Sotalol, flecainide (both C)	-	Ventricular arrhythmia	Withdrawn	Arrhythmia ventri-cular, off-labeluse, Pacing threshold decreased*	Unknown
2	76/M	Hypertension, electrical cardioversion	Dronedarone (S) Ramipril, hydrochlorothiazide, phenprocoumon, tamsulosin (all C)	17days to first recorded episode	Atrial fibrillation	Withdrawn after recurring episodes	Arrhythmia ventricular, tachycardia ventricular	Recovered
3	71/F	Type 2 diabetes Mellitus	Dronedarone (S) Simvastatin, candesartan, metoprolol, phenprocoumon (all C)	-	Cardiac ablation	Unknown	Arrhythmia ventricular	Recovered
4	75/M	Merkel cell carcinoma previously in chemotherapy	Dronedarone (S) Betablocking agents, ceftriaxone, paracetamol, enoxaparin, oxycodone, vancomycin (all C)	21days	Atrial flutter	Dosenot changed	Arrhythmia ventricular, sudden death	Died

**term in MedDRA*

Table 2. Characteristics of 29 reports for dronedarone and ventricular fibrillation in VigiBase®

Case	Age/ Sex	Medical history	Suspected (S) and concomitant (C) drugs	Time to onset	Indication	Action Drug	ADR terms (WHO-ART)	Outcome
1	68/M	Dilated cardiomyo- pathy, left BBB, HF with ejection fraction decreased,, tachy- arrhythmia abso- luta, atrial fibrillation, coronary sclerosis, hyperthyroidism, nodular goiter	Dronedarone (S) Digoxin, phenprocoumon, ramipril, acetylsalicylic acid, fluoxetine, enoxaparin, spironolactone, bisoprolol, simvastatin, furosemide (all C)	0 days	Cardiac arrhythmia	Withdrawn	Fibrillation ventricular	Recovered
2	87/M	CKD, tuberculosis, COPD, ostheo- arthritis, pacemaker user (biventricular), dyslipidemia, T2DM, isquemic cardiomyo- pathy, hypertension, HF, chronicatrial fibrillation, coronary artery bypass	Dronedarone, mexiletine, amiodarone (all S) Guaifensin, digoxin, warfarin, prednisone, simvastatin, mometasone, furosemide, macrogol, metoprolol, glibenclamide, calcium carbonate, diazepam, spironolactone, colchicine, allopurinol, zolpidem (all C)	0 days	Ventricular tachycardia	N/A	Fibrillation ventricular, tachycardia ventricular, QT prolonged, cardiac arrest, off-labeluse	Died
3	55/F	Valvular heart disease, cardiomyopathy	Dronedarone (S)	-	Atrial fibrillation	Withdrawn	Fibrillation ventri- cular, torsadede pointes, QT pro- longed, cardiomyo- pathy, heartvalve disorders, fibrillation atrial, hemothorax, thrombocytopenia, fall, anaemia	Recovered
4	-/-	-	Dronedarone (S)	6 days	Atrial fibrillation	Unknown	Fibrillation ventricular	Unknown
5	71/M	Alcohol use, left ventricular dysfunction, cardiomyopathy	Dronedarone (S) Gabapentine, metoprolol, lisinopril, folic acid, warfarin, calcium channel blockers (all C)	111 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, encephalopathy anoxic	Died
6	68/M	Hypertension, coronary artery disease, mitral regurgitation, dilated cardiomyopathy	Dronedarone (S) Furosemide, lisinopril, carvedilol (all C)	31 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, QT prolonged	Recovered

7	74/M	-	Dronedarone (S) Bisoprolol, acetylsalicylic acid, atorvastatin, warfarin, furosemide, candesartan (all C)	-	Ventricular fibrillation	Unknown	Fibrillation ventricular, breath shortness, cardiac failure, condition aggravated, intolerance induced, off-label use	Unknown
8	-/M	Dilated cardiomyopathy, implantable cardioverter defibrillator user	Dronedarone (S)	4 days	Ventricular arrhythmia	Withdrawn	Fibrillation ventri- cular, implantable defibrillator malfun- ction*, off-label use	Recovered
9	65/M	Atrial fibrillation at arrhythmia absoluta, sick sinus syndrome moderate adiposi- tas, hypertension with left ventricular hypertrophy, dilated cardiomyopathy, HF NYHA II, ventricular	Dronedarone (S) Phenprocoumon (C)	-	Atrial fibrillation	Withdrawn	Fibrillation ventricular, death	Died
10	-/M	Pacemaker user, hypercholesterole- mia, hereditary hae- morragic telangiecta- sia, atrial fibrillation, anemia, edema	Dronedarone, ethanol (both S) Atorvastatin, potassium, warfarin, iron, furosemide (all C)	159 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, tachycardia ventricular, QT prolonged, cardiac arrest, hypokalaemia	Recovered
11	78/M	Melanoma, HF, asthma	Dronedarone (S) Digitoxin (C)	6 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, resuscitation*	Recovered
12	25/M	-	Dronedarone (S) Digoxin, escitalopram, furosemide, sildenafil, lorazepam, multivitamins with minerals, diphenydramine, metoprolol, paracetamol/ hydrocodone, epoprostenol (all C)	-	Atrial fibrillation	Withdrawn	Fibrillation ventricular, tachycardia ventricular, collapse transient, right BBB*	Unknown

13	69/M	Carotid arteriosde-rosis, hyperkalemia, acute renal failure, colon carcinoma, transit ischemic attack, cardioversion, mitral valve incompe-tence, aortic sclero-sis, anemia, steroid	Dronedarone, theophylline (both S) Prednisolone (C)	~186 days	Extrasystol es	Withdrawn	Fibrillation ventricular, coma, ECG abnormal, torsade de pointes, QT prolonged, hypokalaemia, extrasystole ventricular, atrial fibrillation, off-label use	Recovering
14	25/M	-	Dronedarone (S) Metoprolol (C)	Within a month	Ventricular fibrillation	Withdrawn	Fibrillation ventricular, tachycardia ventricular, extrasystole ventricular, fatigue, off label use	Recovered
15	46/F	Hypothyroidism, T2DM, muscular dystrophy, atrial fibrillation, atrial tachycardia	Dronedarone (S) Enoxaparin, metoprolol, metformin, warfarin, thyroid therapy, ibuprofen, paracetamol (all C)	2 days	Atrial fibrillation	N/A	Fibrillation ventricular, fatigue	Died
16	49/F	Implantable cardioverter defibrillator user	Dronedarone (S)	28 days	Atrial fibrillation	Unknown	Fibrillation ventricular, torsade de pointes	Unknown
17	59/F	Dilated cardiomyopa- thy ejection fraction 36%, lung cancer, hypertension, HF NYHA II-III. implan-table cardioverter defibrillator user	Dronedarone (S) Furosemide, ezetimibe, sertraline, carvedilol, iron, valsartan, eplerenone, acetyl- salicylic acid, linum usitatis-simum (all C)	2,5 months to first recorded episode	Ventricular arrhythmia	Withdrawn after second episode	Fibrillation ventricular, tachycardia ventricular, off-label use	Recovered
18	50/M	HF, implantable cardioverter defibrillator user	Dronedarone (S)	14 days	Atrial flutter	Withdrawn	Fibrillation ventricular, QT prolonged	Recovered

19	59/F	Hypertension, obesity, HF, CKD stage III	Dronedarone (S) Diltiazem, spironolactone, ramipril, simvastatin, furose- mide (all C)	-	Atrial fibrillation	Withdrawn	Fibrillation ventri- cular, tachycardia ventricular, QT prolonged, cardiac arrest, hypoxic-ischaemic encepha- lopathy*	Died
20	88/F	Congestive HF, CKD, COPD, coronary artery disease, T2DM, hyperlipidmia, hypothyroidism, gastroesophageal reflux disease	Dronedarone, levofloxacin (both S) Diltiazem, digoxin, glyceryl trinitrate, salbutamol, clopi- dogrel, cilostazol (total 29 medical products, all C)	1 day	Atrial fibrillation	N/A	Fibrillation ventricular, tachycardia ventricular, torsade de pointes	Died
21	77/F	Tachycardia-bradycardia syndrome, pacemaker user (dual chamber), dilated cardiomyopathy with ejection fraction 69%, asthma, obesity	Dronedarone (S) Calcium, docusate, diltiazem, ergocalciferol, levosalbutamol, alendronic acid, estradiol, vitamins, acetylsalicylic acid, spironolactone, fluticasone, atorvastatin, levothyroxine, furosemide (all C)	446 days	Atrial fibrillation	Withdrawn	Fibrillation ventri- cular, torsade de pointes, QT pro- longed, cardiac arrest	Recovered
22	80/M	-	Dronedarone, quetiapine (both S) Acetylsalicylic acid, warfarin (both C)	128 days	Atrial fibrillation	Withdrawn	Fibrillation ventri- cular, QT prolonged, hypertension, drug interaction, hae- maturia	Recovering
23	67/M	Previous episodes of ventricular arrhythmia, cardiac ablation, bronchitis, ischemic heart disease	Dronedarone, amoxicillin (both S) Metoprolol, rosuvastatin, clopidogrel, ubidecarenone, famotidine, warfarin, enoxa- parin (all C)	-	Ventricular fibrillation	Continued	Fibrillation ventricular, anxiety, extrasystoles, dyspepsia, tachycardia, off- label use	Unknown
24	79/M	Tachycardia-bradycardia syn- drome, sick sinus syndrome, CKD, hypertension, T2DM, coronary artery disease, previous myocardial infarction	Dronedarone (S) Isosorbide mononitrate, lisinopril, simvastatin, meto- prolol, vitamins, acetylsalicylic acid, cimetidine, furosemide, insulin (all C)	170 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, torsade de pointes, QT prolonged	Recovered

25	73/M	Previous episodes of premature ventricular contractions, bifascicular block, normal left ventricular function	Dronedarone, metoprolol (both S) Zolpidem, digoxin, iron, acetylsalicylic acid (all C)	144 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular	Died
26	51/M	Elevated lipids	Dronedarone (S) Antipropulsives, warfarin (both C)	46 days	Atrial fibrillation	Withdrawn	Fibrillation ventricular, ejection fraction abnormal, diarrhoea, neurologic disorder, syncope, hypomagnesaemia, hypokalaemia, hepatic function abnormal	Died
27	58/F	Ventricular tachycardia, non ischemic dilated cardiomyopathy, left BBB, premature ventricular tachycardia, hyperlipidemia, HF with ejection fraction 35%	Dronedarone (S) Atenolol, hydrochlorothiazide/triamterene, furosemide, tranylcypromine, quinapril, warfarin, folic acid (all C)	36 days	Atrial fibrillation and ventricular arrhythmia	N/A	Fibrillation ventricular, coma, cardiac arrest, respiratory arrest, hypoxic-ischaemic encephalopathy*	Died
28	72/F	-	Dronedarone (S)	-	Atrial fibrillation	Withdrawn	Fibrillation ventricular, torsade de pointes, QT prolonged, tachycardia ventricular	No effect observed
29	70/M	Tachycardia-bradycardia syndrome, pacemaker user, surgical revascularization, ischemic cardiomyopathy	Dronedarone (S) Omeprazol, rosuvastatin, warfarin, acetylsalicylic acid, nicotinic acid (all C)	190 days	-	N/A	Fibrillation ventricular, myocardial infarction	Died

*Abbreviations: BBB - bundle branch block, HF - Heart failure, CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease, T2DM - type 2 diabetes mellitus, N/A - not applicable *terms in MedDRA*

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Response from Sanofi

The main safety concern with antiarrhythmics particularly with Class I and III, is the potential proarrhythmic effect. The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation linked to the therapeutic effect of dronedarone and does not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped. Based on clinical experience, dronedarone has a low proarrhythmic effect. However, proarrhythmic effects may occur in particular situations such as concomitant use with medications favouring arrhythmia and/or electrolytic disorders. That information is translated into the contraindications and precautions for use of dronedarone Product Information worldwide.

After the early termination of the PALLAS study due to excess of cardiovascular events in the dronedarone group, the use in permanent AF patients was contraindicated and serial ECGs were recommended, additional risk minimisation measures were implemented in the Risk Management Plan.

Close surveillance of proarrhythmic effects ventricular arrhythmia (NOS) and cardiac death cases has been performed via routine pharmacovigilance, namely in Periodic Safety Update Reports (PSURs). From periodic analyses and review of such cases and based on the information collected from product launch to last PSUR (31 July 2013), no new safety information with regards this topic was raised. The EMA endorsed this conclusion in its assessment of the last submitted PSUR.

From launch to 31 July 2014 the MAH has collected worldwide 227 cases referring to ventricular tachyarrhythmia using the standardized MedDRA query version 17.0 "Ventricular tachyarrhythmia_Narrow", and 60 cases referring to cardiac or cardio-respiratory Arrest.

Overall, the review and analysis of all the cases of ventricular tachycardia, torsade de pointes and cardiac arrest showed that contributive factors such as concomitant drugs and or underlying cardiac disease were reported; or cases were poorly documented to allow proper medical assessment.

Focusing on the cases reported in the publication, the safety database retrieved 11 cases of ventricular arrhythmia/tachyarrhythmia and 40 cases of ventricular fibrillation, they are analyzed below :

Ventricular arrhythmia(VA)/ tachyarrhythmia cases(n=11):

They originated from Germany (n=4), United States (n=3), France (n=2), Italy and Sweden (n=1 each), involved 7 men and 4 women. One case was solicited and 10 were unsolicited. Two patients were <65 years, unknown age (n=1), elderly >70 years (n=8), (mean 71.7 years). Time to onset was available in 4 cases, all but 1 within 1 month. Outcome was favorable (n=5), all after dronedarone discontinuation; unknown (n=5), fatal (n=1). Ventricular tachycardia was co-reported in 3 cases, sudden death and cardiac arrest in 1 case each.

Among 9 documented cases, in all reported concomitant treatments with potential cardiac effects, and 8 relevant medical history/concomitant diseases, and information on electrolyte abnormalities, thyroid status, was missing in all but 1 case.

- In the case of sudden death, the death is likely resulting from a malignant ventricular arrhythmia given the patient's carcinoma, the instantaneous nature of death and recent arrhythmias.
- In the case of cardiac arrest, concomitant use of amiodarone by error was reported, the patient recovered while dronedarone was pursued.

Concerning ventricular fibrillation(VF) cases(n=40)

They originated from mainly from United States (n=25) and Germany (n=5), involved 30 men, 8 women (unknown gender in 2 cases). Nine cases were solicited and 31 were unsolicited. Seventeen patients were <65 years, elderly (n=11), elderly >75 years(n=9), and unknown(n=3), (mean 64.2 years). Time to onset was available in 25 cases, from few hours to 8.5 months and within 1 month in 13 cases. Outcome was recovered/recovering (n=21) (following dronedarone withdrawal (n=14), pursued(n=4); not applicable (n=2), and unknown (n=1)); unknown(n=3); and fatal(n=16). Ventricular tachycardia was co-reported (n=9), torsade de pointes (n=5) ; cardiac arrest(n=6), and sudden death(n=4).

7.2 Serious QT interval prolongation with ranolazine and amiodarone

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Letter to the Editor

Serious QT interval prolongation with ranolazine and amiodarone

Mónica Tarapués [a,*], Gloria Cereza [a,c,d], Ana Lucía Arellano [b], Eva Montané [a,b], Albert Figueras [a,c]

[a] Pharmacology, Therapeutics and Toxicology Department, UniversitatAutònoma de Barcelona, 08193 Bellaterra (Cerdanyola del Vallès), Spain
[b] Clinical Pharmacology Department, Hospital Universitari Germans TriasiPujol, Carretera de Canyet s/n, 08916 Badalona, Spain
[c] FundaciólnstitutCatalà de Farmacologia, PasseigVall'Hebron 119-129, 08035 Barcelona, Spain
[d] Catalan Centre of Pharmacovigilance, Barcelona, Spain

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To the Editor:

QT interval prolongation is an adverse drug reaction (ADR) associated with some antiarrhythmic and non-antiarrhythmic drugs. This ADR can lead to ventricular tachyarrhythmia and *Torsade de Pointes* (TdP) [1].

We report the case of a 78 year-old woman who developed an unusual episode of TdP in the context of the use of ranolazine and amiodarone. In June 2010, the patient was admitted to the emergency department because of worsening angina, dyspnoea and orthopnea. Three days before she was prescribed ranolazine of 375 mg/12 h by her family doctor. Blood tests did not show any electrolyte abnormality, but the ECG tracing showed slow atrial fibrillation (AF) with nodal rhythm (50 bpm), bigeminism and frequent ventricular extrasystoles. She stayed under observation, and few hours later, developed two episodes of polymorphic nonsustained ventricular tachycardia (NSVT), thereafter intravenous amiodarone was started. Despite of the amiodarone, the NSVT evolved to polymorphic sustained ventricular tachycardia (*Torsade de Pointes*) that required a 200 J cardiac defibrillation. The ECG showed a narrowing QRS complex, nodal rhythm (50 bpm) and prolonged QTc interval (580 msec).

The past medical history of the patient included diabetes, dyslipidemia, hypertension, severe chronic renal failure (GFR: 28 ml/min), AF, ischemic heart disease and heart failure. She had been admitted to the hospital throughout the previous 6 months for several episodes of acute heart failure secondary to rapid AF and/or angina. She was in treatment with aspirin, topiramate, simvastatin, furosemide, omeprazole, acenocoumarol, nitro-glycerine, hydralazine, glicazide and allopurinol.

In the current hospitalization, the patient was admitted in the intensive care unit. None significant injury was found in heart catheterization. The echocardiogram showed a slightly dilated and hypertrophied left ventricle with inferior hypocinesia, a severe mitral valve regurgitation, and an ejection fraction of 37%, similar to the one recorded in January-2010. Finally, her cardiac rhythm in AF was recovered with low doses of β-blockers. The QT interval was gradually normalized, without new arrhythmic events. Ranolazine and amiodarone were withdrawn.

TdP is related to the QT interval prolongation usually due to the inhibition of the rapid outward potassium currents (IKr)[1]. Amiodarone is a multichannel antiarrhythmic drug with the lowest incidence rate of TdP. (< 1%) [1,2]. However some clinical conditions (e.g., electrolyte disorders, bradycardia and concomitant administration of drugs with high proarrhythmic risk) and concomitant use of amiodarone have been associated to an increased of the risk of TdP [3,4]. Moreover amiodarone is metabolized by cytochrome P-450 (CYP3A4)[4]. The interaction profile of this drug is mainly associated with its inhibitory activity, but amiodarone is also a substrate of CYP3A4. Therefore drugs that inhibit this isoenzyme could increase the concentration of amiodarone. It has been suggested that the concomitant use of amiodarone and metronidazol could produce cardiac toxicity due to CYP3A4 inhibition [5].

Ranolazine is a new second-line drug recommended in patients with stable angina inadequately controlled or intolerant to first-line drugs. Ranolazine produces myocardial relaxation through inhibition of the delayed current of sodium. Its use should be avoided in severe renal impairment due to a 2-fold AUC increase [6,7]. Ranolazine has a theoretical risk of developing TdP due to the inhibition of IKr channels in high doses and therefore the enlargement of QT interval. Pivotal clinical studies of ranolazine showed 2 cases of TdP (placebo and ranolazine group, one each) [6,8]. Thus, its use is contraindicated in patients with high risk of QT interval prolongation, and it is not recommended to be used in association with other QT interval prolonging drugs such as class Ia and III antiarrhythmic; except amiodarone [6].

In addition, ranolazine is a substrate of cytochrome P-450 (CYP 3A4), and has been reported as a mild inhibitor of CYP3A4 and P-glycoprotein; for this reason its interaction profile includes a warning about increased concentrations of simvastatin, and suggests a careful use with other substrates of CYP3A4 [6]. Recently, it has published a case of high plasma concentrations of tacrolimus (substrate of CYP3A4) attributed to the inhibition of cytochrome P-450 induced by ranolazine [9].

* Corresponding author.
E-mail address: mtr@icf.uab.cat (M. Tarapués).

A recent study has shown the efficacy of ranolazine + amiodarone in the treatment of supraventricular arrhythmia and it has been suggested that the combination of these two drugs does not increase the risk of arrhythmic events [10]. However it should be highlighted that all patients with high cardiac risk or with prior exposure to ranolazine were excluded. Thus, the safety of this combination remains unclear and some large studies are currently ongoing [11].

In our case, the patient had cardiac risk factors that could contribute to the appearance of TdP, despite this, the strong temporal relation between ranolazine + amiodarone administration and the TdP episode suggests a potential causal relationship. Moreover an inappropriate use of ranolazine (the patient's severe renal impairment was overlooked) could increase the exposure to the drug. This high ranolazine plasma concentration may have affected the metabolism of intravenous amiodarone, and this drug interaction could have produced QT interval prolongation and TdP. The feasible inhibition of potassium channels due to amiodarone and ranolazine together should not be excluded.

The case described herein together with the current knowledge about these drugs suggests that amiodarone + ranolazine should be only prescribed in patients without cardiac and/or renal risk factors. Ranolazine is a new drug; thereby its interaction profile and the potential risk of TdP remain unknown. Clinicians should be aware of this possible interaction, keeping in mind that sometimes the inappropriate use of drugs could precipitate a serious ADR.

Contributions of authors statement

EM and AIA have recovered the patient's complete medical history, upon the request of the Spanish Pharmacovigilance System (SPvS). MT identified and assessed the described cases in the SPvS database. She searched literature related Ranolazine safety and wrote the first draft. EM, GC and AF have contributed to the first draft with relevant comments. GC, AF and MT made corrections to the final version.

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7.3 New statins also produce Fatigue: Spontaneous reporting as a complementary system to increase safety knowledge

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New Statins Also Produce Fatigue: Spontaneous Reporting as a Complementary System to Increase Safety Knowledge

We have read with interest the Research Letter by Golomb et al[1] about the effects of statins on energy and fatigue with exertion. The Research Letter describes the first randomized evidence of these adverse drug reactions (ADRs) for simvastatin and pravastatin, previously reported as anecdotal cases in the literature. The study attracted our attention because it has tied up loose ends after signal detection by pharmacovigilance systems based on spontaneous reporting. Notwithstanding, at the same time it has been a stimulus to look for new data after posing the question "Do the new statins also produce these adverse effects?"

We have reviewed the Spanish Pharmacovigilance System database, which contains more than 193 000 reports of suspected ADRs collected since 1984. The reports involving rosuvastatin (marketed in 2009) had been retrieved and carefully analyzed. Of 263 reports, 9 described asthenia (4 cases), loss of muscular strength (4 cases), or fatigue (1 case) as isolated symptoms (not related with either muscle pain or increase in creatine kinase level). It is to be noted that 6 of 9 patients were younger than 65 years, and 5 of 9 were women taking 5 to 20 mg daily, who had roughly 3 weeks of exposure before the appearance of the ADR. Pitavastatin was marketed in 2011; until March 2012, only 23 reports had been received, and no case of energy or exertional fatigue has been reported.

Musculoskeletal disorders are well-known ADRs of this group of cholesterol-lowering treatments, and severe cases presenting rhabdomyolysis and increase in creatine kinase level have been fully described.[2] Mild cases and intolerance to exercise by young athletes have also been described.[3,4] Notwithstanding, in our opinion it is important that prescribers keep in mind the possibility that any statin treatment produces these symptoms, especially because they also appear in young patients (ie, those prone to practice any sport).

Whenever possible, the pharmacological treatment of hyperlipidemia should be accompanied by a nonpharmacological approach (eg, to avoid a sedentary life and to exercise). If unnoticed, these ADRs of statins could prevent the benefits of exercise because of fatigue and pain, so knowledge of these adverse reactions of new drugs improves treatment objectives. However, health professionals continue to play an essential role in completing the safety profile of any new drug through ADR reports. In the case of statins, by following these traditional steps we can improve the efficiency and effectiveness of the comprehensive approach to the patient with increased blood cholesterol levels.

Mónica Tarapués, MD
Gloria Cereza, MD
Albert Figueras, MD

Author Affiliations: Department of Pharmacology, Therapeutics, and Toxicology, Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Spain (Drs Tarapués and Figueras); Fundació Institut Català de Farmacologia, Barcelona, Spain (Drs Cereza and Figueras); and Catalan Centre of Pharmacovigilance, Spanish Pharmacovigilance System, Barcelona (Dr Cereza).
Correspondence: Dr Figueras, Fundació Institut Català de Farmacologia, Hospital Vall d'Hebron 119-129, E-08035 Barcelona, Spain (afs@icf.uab.cat).

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In reply

We concur with Tarapués and colleagues. An analysis we conducted of patient reports of muscle problems (including fatigue)[1] is in agreement with their Spanish data, extending fatigue adverse effects (AEs) to all statins. These data suggest that risk approximately parallels statin potency, as does our recent analysis of the US Food and Drug Administration AE reports focused on muscle-related AEs,[2] although this latter analysis did not expressly address fatigue.

We agree that AE reporting by physicians is important. We add that patient reporting is important as well. Physicians sometimes dismiss a drug relationship for AEs unfamiliar to them.[3] Heeding patient reports has been shown to lead to the same AEs being identified, but often sooner.[4] Patient reports and attributions of AEs have been found to be generally reliable, and the European Union has recently adopted patient reporting for all its pharmacovigilance databases (http://ec.europa.eu/health/human-use/pharmacovigilance/developments/index_en.htm). Because statins can have bidirectional effects on many outcomes (eg, causing or protecting against proteinuria) that are associated with variable predominance of prooxidant vs antioxidant effects,[5,6] randomized controlled trials (RCTs) can miss causal AE occurrence. Moreover, RCT participant selection practices may lead persons most at risk of AEs to be excluded. Adverse events that may be focused in cer-

tain participant groups (owing to "effect modification") are important to recognize, even when the average observed effect of a drug has not been noted to be deleterious—in the RCT samples thus far examined. The impact to the person experiencing a problem is real whether or not the effect is "typical," and recognition of the possible connection to the drug is essential to enable actions to be taken (like drug discontinuation) that may reduce ultimate disability. In short, we concur that AE reports can presumptively identify AEs before they are identified in an RCT setting and add that including patient reports may hasten this.

Finally, Tarapués et al observe that "these ADRs of statins could prevent the benefits of exercise" and urge that exercise accompany statin use. A caveat to this excellent point is that, in the setting of mitochondrial compromise, which statins can foster,[5] exercise may worsen the energy supply-demand imbalance, potentiating risk (or severity) of statin muscle injury. This is another reason to focus statin use (indeed, preventive drug use generally) in those for whom evidence shows definite expectation of net benefit to the patient, judged by outcomes, such as all-cause mortality, that objectively balance risk and benefit.

Beatrice A. Golomb, MD, PhD
Sabrina Koperski, BS

Author Affiliations: Departments of Medicine (Dr Golomb and Ms Koperski) and Family and Preventive Medicine (Dr Golomb), University of California, San Diego, La Jolla.
Correspondence: Dr Golomb, Department of Medicine, University of California, San Diego, 9500 Gilman Dr, Mail Code 0995, La Jolla, CA 92093 (bgolomb@ucsd.edu).
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Jehovah's Witnesses May Not Have Identical Outcomes With Nontransfused Non-Witnesses After Cardiac Surgery

In an attempt to investigate the effect of current extreme blood management strategies on outcome of patients undergoing cardiac surgery, Pattakos et al[1] used, what they called, the "natural experiment" of Jehovah's Witnesses, who refuse blood transfusions owing to religious beliefs.[1] They performed a statistically elaborate analysis of operative and long-term outcomes in Witnesses compared with propensity-matched patients who received transfusions. They concluded that extreme blood management strategies do not appear to place patients at heightened risk for operative mortality and morbidity nor reduce their long-term survival.[1] As a matter of fact, their analysis demonstrated that Witnesses had a relatively improved overall outcome, ie, a lower operative morbidity and, in long-term follow-up, a lower risk of death in the early hazard phase. Hence, this report corroborates other observational studies indicating that transfusions are associated with negative outcomes following cardiac operations.[2,3]

Nonrandomized studies suffer from the uncertainty of potential unmeasured patient or procedure-related variables influencing the results.[4] Besides unknown confounders, however, an inherent lurking variable should be considered in this study: religious belief per se. There is some evidence suggesting a conscious or subconscious modification of operative technique to ensure better hemostasis in Jehovah's Witnesses. Despite "postoperative liberal use of additional operation for bleeding"[1(p1154)] that the authors state as one of blood conservation practices, Witnesses were not taken back to the operating room more frequently than non-Witnesses. Contrariwise, non-Witnesses were nearly twice as likely to undergo additional operation for bleeding or tamponade (7.1% vs 3.7% in matched groups; $P=.03$).[1] Intriguingly, perioperative myocardial infarction was also significantly more frequent in non-Witnesses (2.8% vs 0.3% in matched groups; $P=.01$).[1] More meticulously performed anastomoses with the intent to be more hemostatic may plausibly account for this difference. Obviously, extra meticulous operative technique can be a key factor affecting operative and long-term outcome.

It would be interesting to know whether the results attained in Jehovah's Witnesses are identical to matched non-Witnesses who were not transfused. Lack of pertinent data casts doubt on the external validity and, hence, the final conclusion of the study. Operative and long-term outcomes of patients who are not eventually transfused do not necessarily match outcomes of patients for whom transfusions are not permitted.

Dimitrios C. Angouras, MD

Author Affiliation: Department of Cardiac Surgery, Athens University School of Medicine, Attikon University Hospital, Athens, Greece.
Correspondence: Dr Angouras, Department of Cardiac Surgery, Athens University School of Medicine, Attikon University Hospital, 1 Rimini St, Chaidari, Athens 12462, Greece (dangouras@yahoo.com).
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