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Sighing by Ticagrelor: Inducing Theoretical Concepts for General Medicine from a Case Study

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Abstract

The problem of adverse drug reactions is one of the most socially relevant in all countries. The position of the general practitioner (GP) who maintains continuous attention observing what happens over time is ideal to be able to detect adverse drug reactions. The new clinical guidelines on the approach to acute coronary syndrome without ST-segment elevation recommend the use of ticagrelor or prasugrel, and only clopidogrel when the former are not available or are contraindicated. However, dyspnea is seen more frequently in patients treated with ticagrelor. In addition, the presence of dyspnea in patients with acute coronary syndrome is always a complex clinical situation. In this context, a case of paroxysmal "sighing" episodes that occurred when falling asleep, in a patient who began treatment with ticagrelor, is presented, with the aim of reflecting and inducing important theoretical concepts for the body of knowledge of general medicine. The case leads us the follow conclusions that are important concepts for GPs: 1) the importance of presenting case reports in the medical culture is forgotten; 2) an important role of the daily work of the GPs is to observe the real life in front of the life taken from a "clinical trial"; 3) GP performing continuous care may observe adverse drug reactions; 4) The symptoms are expressions of the patient, and the GP must remain attentive to understand them; 5) The meaning of experiencing dyspnoea is difficult to explain on the part of the patient and to understand the part of the doctor; 6) When an unexplained symptom is observed within the usual theoretical frameworks, think of adverse reactions to drugs; 7) When faced with an unexplained symptom that could be an adverse reaction, do not treat it with another drug; and 8) The frequency of dyspnoea with ticagrelor is sufficiently high to be alert when prescribing this drug.

Keywords

Family physician; Family practice; Acute Coronary Syndromes; Antiplatelet; Ticagrelor; Dyspnoea; Adverse Effects

Introduction

Clinical guidelines for antiplatelet therapy in patients with the acute coronary syndrome are changing to the use of ticagrelor because of the mortality benefits demonstrated in the trials compared to clopidogrel. But, in clinical trials dyspnoea is found more frequently in patients prescribed ticagrelor *vs.* clopidogrel, and rates are higher than previously reported, requiring the dyspnoea in some patients a change in drug therapy, and this is associated with readmission to the hospital. However, since ticagrelor is most commonly used, the incidence of dyspnoea may still have even higher rates, as well as drug discontinuation, re-hospitalization, and possible treatment failures, than informed in the controlled design of clinical trials [1].

Pharmacovigilance can be defined as the study of the safety of drugs in the conditions of use of the clinical practice in large communities. Thus, pharmacovigilance is, strictly speaking, a public health activity aimed at analyzing and managing the risks of medicines once marketed. The greatest importance of pharmacovigilance lies in the fact that a new drug has been registered does not mean that everything is known about it: pre-commercial clinical trials are carried out in a number of patients that is insufficient to detect a reaction adverse rare: it is enough to think that to detect three cases of an adverse reaction whose incidence is 0.1% are necessary 6,500 patients, while this number increases to 65,000 patients in the event that the incidence of adverse reaction is 0.01%. In addition, pre-commercialization clinical trials are carried out under very standardized conditions, which limit the extrapolation of the results to the usual conditions of use. Thus, in usual practice, the number of patients exposed to treatment is much greater than in clinical trials, the duration of treatment may be longer, special populations not specifically studied during clinical development may be treated, the concomitant pathology is more frequent, the possibility of interactions is greater and therapeutic compliance is not controlled in the same way.

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For these reasons, it is clear that, when prescribing a pharmacological treatment, the physician may face new situations in daily practice different from those previously reflected in the literature and may observe and/or suspect adverse reactions so far unknown or that, even if being known, they imply an increase in the incidence and/or severity, which provides an undoubtedly important knowledge [2].

The position of the general practitioner (GP) who is not only involved in treating and preventing the disease and promoting health, but maintains continuous attention, acting as a witness to the patient's experience, and observing what happens over time, is ideal for be able to detect adverse reactions to medicines [3]. In these circumstances, the role of the GP reflective and attentive is crucial, so as to illuminate the clinical path of the patient without being dazzled by the new prescriptions [4].

In this context, we present a case of paroxysmal "sighing" episodes that occurred when falling asleep, in a patient who began treatment with ticagrelor, with the aim of reflecting and inducing important theoretical concepts for the body of knowledge of general medicine and its practical application.

Clinical Observation

A 75-year-old man with chronic obstructive pulmonary disease and chronic kidney disease (creatinine of 2.23 mg/dl) was admitted in hospital for stable angina on May 25, 2018. In the emergency department, he was given a loading dose of acetylsalicylic acid and ticagrelor. Troponin I normal, Echo cardiogram with normal LVEF and without segmental alterations. After prophylaxis of contrast nephropathy, coronary angiography was performed with a severe lesion in Posterior Descending coronary artery that was treated with Percutaneous Coronary Intervention and drug-eluting stent. He was discharged in a good clinical situation and stable renal function with the main diagnosis of Non-ST-Elevation Acute Coronary Syndrome, type unstable angina. Was prescribed the following treatment:

-Acetylsalicylic acid 100 mg, 1 tablet in midday meal

-Ticagrelor 90 mg, 1 tablet at breakfast and dinner, for one year

-Omeprazole 20 mg, 1 capsule at breakfast

-Rosuvastatin 10 mg, 1 tablet at dinner

-Bisoprolol 2.5 mg, 1/2 tablet at breakfast

The patient consulted on June 15, 2018, to his GP for "sighs" that "arise when he falls asleep on the couch." The patient reports that "he falls asleep watching TV ... and wakes up suddenly because he has to give a sigh because he drowns ...". This symptom also occurs at night. "So he's afraid to fall asleep ..." Observation is decided thinking about anxiety. The patient consulted again on June 24, 2018, for the persistence of sighs when falling asleep. He refuses to present anxiety. "It is necessary to give me treatment, since I cannot fall asleep for fear of sighing because of lack of air, and so I cannot continue, because I am tired ...", said the patient. He was treated with Dexchlorpheniramine (an antihistamine), still thinking about anxiety and trying to avoid using a benzodiazepine. But the patient does not improve and on July 19, 2018, about a month and a half after his Non-ST-Elevation Acute Coronary Syndrome type unstable angina, and after to start with the new treatment, Ticagrelor is suspended and changed to Prasugrel; the sighs disappearing.

Discussion

The problem of the use of medications is one of the most socially relevant in all countries, and adverse drug reactions are an important part of this problem, being frequent in clinical practice. An adverse reaction to drugs is "any response to a drug that is harmful and unintentional, and that takes place at doses that are normally applied in humans for the prophylaxis, diagnosis or treatment of diseases, or for restoration, correction or modification of physiological functions." As a counterpart of its effectiveness, medicines have the price of the possibility of producing adverse effects [5].

The natural history of the disease refers to the clinical course of a morbid process. General medicine is a very good opportunity to study the natural history of a disease [6]. In general medicine, every contact with patients provides opportunities for medical intervention, including the detection of adverse reactions to drugs. Therefore, the attending physician can make a significant contribution to pharmacovigilance on the basis of routinely seen patients [7].

The clinical benefit in antiplatelet treatments has been demonstrated with P2Y receptor antagonists, such as clopidogrel. However, certain problems of this drug, such as the relatively slow onset of its effect, have forced to seek a greater pharmacotherapeutic development. Ticagrelor, a cyclopentyltriazolopyrimidine, is a novel reversible oral P2Y antagonist. This drug differs from thienopyridines (ticlopidine, clopidogrel, prasugrel) in that it is not a pro-drug that requires active biotransformation by cytochromes in the liver and, therefore, is characterized by a faster, more effective and consistent platelet inhibition than ticlopidine or clopidogrel. These properties and the results of clinical trials have led to a change in the approach to antiplatelet therapy. The new clinical guidelines on the treatment of acute coronary syndrome without elevation of the ST segment recommend the use of ticagrelor or prasugrel, despite some limitations, such as the risk of dyspnoea [8-11].

In patients with acute coronary syndrome, the onset of dyspnea can be classified as a complex clinical situation. In recent years, this situation has become more problematic, due to the increasing use of ticagrelor, since this drug can induce dyspnea as an adverse secondary effect [12]. A higher incidence of dyspnoea has been observed in patients treated with ticagrelor (15%) vs. patients treated with clopidogrel (9%), with a severe intensity similar in both groups. This dyspnea related to ticagrelor is usually assessed as mild or moderate and, in patients with acute coronary syndrome does not seem to be associated with differences respect to the efficacy or results of this treatment compared to treatment with clopidogrel [13]. Because dyspnea is not associated with acidosis, pulmonary or cardiac dysfunction, alterations in the mechanisms and pathways of dyspnea may be involved in its pathogenesis [14].

The symptoms can be defined as "any subjective evidence of a health problem as perceived by the patient." Therefore, the symptoms are subjective; they are the result of a process of patient interpretation. The experiences of the symptoms are integrated into a complex interaction between biological, psychological, social and cultural factors. Consequently, it can be said that there is a certain variety of interpretations of the sensations, which are not always equivalent to the expressions of the underlying disease [15]. In this context, the symptom of dyspnoea refers to "shortness of breath" or difficult or uncomfortable breathing sensation. It is a subjective experience that indicates how it is perceived and expressed or reported by an affected patient [16]. Therefore, perhaps even more than other symptoms, due to the psychosocial connotations of "lack of air", or "lack of breathing", or "unbreathable environment", or "asphyxia", and because of what was said above, the subjectivity of the dyspnoea is difficult to assess and is a general term or concept used to characterize a range of qualitatively and quantitative very different situations. The study of the language used could help define one or more of the anomalies responsible for respiratory distress. Because the symptom of dyspnoea is a fundamental element of the patient's medical history, physicians should be able to go deeper into the patient's language that describes dyspnea [17].

Dyspnoea is caused by a variety of physiological, pathophysiological, psychological and environmental factors. The mechanisms that lead to dyspnoea are not fully understood. It is known that mechanical reasons such as alterations of ventilation (obstruction, restriction), deterioration of ventilation muscles, skeletal deformation and many other reasons can cause dyspnoea [18]. Depending on the mechanism involved, dyspnoea can be classified into different types. "Air hunger" is produced from the chemoreflex activity, and inhibited by pulmonary inflation, probably through a reflex originated in the receptors of a stretch of the airways. The sensation of increased respiratory work occurs particularly during volitional breathing and is increased by increased breathing work or muscle weakness. This sensation is probably induced by

S.No	Concepts	Comments
1.	Continuity of Care	The GP can observe the evolution of the health problem
2.	The symptoms	They are expressions of the patient, and the GP must remain attentive to understand them. The meaning of experiencing dyspnoea is difficult to explain on the part of the patient and to understand by the GP
3.	The symptom of paroxysmal sighs when falling asleep	It could be a form of paroxysmal nocturnal dyspnoea
4.	The observation an unexplainable symptom within the usual theoretical frameworks	Review the patient's medication, and think about adverse reactions to drugs, assessing the possible correlation with the introduction of new drugs in the patient, and review the reported and established adverse reactions of the drugs
5.	In the presence of an unexplained symptom that could be an adverse reaction	Do not treat with another drug; remove the drug (possibly or clearly) involved
6.	Dyspnea with ticagrelor	The frequency of dyspnoea with ticagrelor is high enough to be alert when prescribing that drug

Table 1: Conclusions of this case, which are important concepts in general medicine

the activity of the cerebral cortex. Recognize and understand the different types of dyspnoea are important for the interpretation, diagnosis, and treatment of this symptom [19].

One type of breathing difficulty while lying down is nocturnal paroxysmal dyspnoea. This condition of paroxysmal nocturnal dyspnoea causes a person to wake up suddenly during the night, feeling short of breath. The problems caused by this situation vary from tiredness during the day to inability to sleep for more than a few minutes. [20].

The sigh (suspire) is defined as an involuntary inhalation (inspiration) that is 1.5 or 2 times greater than the common lung volume [21]. In the respiratory mechanics of sighing, the upper chest, dorsal muscles, or upper sternum are commonly used [22]. Sighing can occur during sleep in ordinary adults [23]. Sighing means inhaling a lot and a level reduced of brain oxygen. It has been suggested that the sigh of a typical adult is 4 times greater than normal lung volume. Sighing is generally considered to be a symptom of deregulated or abnormal breathing since normal breathing in healthy people is regular or periodic (e.g., without sighs). Frequent or excessive sighing is considered a sign of panic disorder or states of anxiety or depression [24-26]. In this way, in most cases, frequent or excessive sighs indicate a state of stress and thus are usually diagnosed as psychogenic dyspnoea.

In our patient we observed paroxysmal sighs when falling asleep, which are a symptom not explicable within the usual theoretical frameworks, as the patient was not in heart failure, nor had respiratory pathology, nor anxiety, nor were there relevant psychosocial problems that justified the appearance of possible crises of anguish, etc. This situation should serve the GP as a sentinel sign to reflect.

Diagnosis of the cause of dyspnoea can be made relatively easily in the presence of other clinical signs of heart or lung disease. The difficulty is sometimes encountered in determining the precipitating cause of breathlessness in a patient with both cardiac and pulmonary conditions. An additional diagnostic problem may be the presence of anxiety or other emotional disorder. A careful history and physical examination are always helpful, and occasionally cardiac catheterization, pulmonary function studies, or other tests may be necessary [16]. The typical approach of current biomedicine is to suppress the symptom (whatever the cost, even if adverse effects occur), but it is ignored that the symptom is only a signal, and sometimes appropriate.

It has been reported in the Technical Data Sheet of ticagrelor, in its adverse reactions section, that the adverse events related to dyspnoea (dyspnoea, dyspnoea at rest, dyspnoea on exertion, paroxysmal nocturnal dyspnoea and nocturnal dyspnoea), as a whole, were recorded in 14% of patients; that is, dyspnoea related to ticagrelor appears in a significant proportion of patients in the first days of its administration. This dyspnoea is usually of mild or moderate intensity and often disappears without the need to interrupt the treatment, and is recorded as an isolated episode shortly after the start of treatment. Patients with asthma/chronic obstructive pulmonary disease may have an increased absolute risk of dyspnoea with ticagrelor. If a patient reports, on the onset with this drug, prolongation or worsening of dyspnoea, an investigation should be conducted and if ticagrelor is not tolerated, treatment should be discontinued [27,28].

These data coincide with the reports on dyspnoea related to ticagrelor in a real population and its implication for the withdrawal of the drug in patients with acute coronary syndrome. All the cases appeared in the first week of starting the treatment, and in 70% in the first 24 hours. In almost all, it was paroxysmal and of light intensity. Some cases lasted less than 24 hours while others persisted over time, presenting most cases paroxysmal [29].

Given the relatively long duration of the symptom of sighs/paroxysmal nocturnal dyspnoea in our patient, it would have been possible to erroneously consider treatments for the symptom of dyspnea, including opioids, benzodiazepines, furosemide, and selective serotonin reuptake inhibitors [30], which could have created a cascade of adverse reactions.

Conclusion

This article could be understood as the presentation of an infrequent case, but one that helps us to understand more important issues and from which we can induce important concepts for general medicine. Sometimes the importance of presenting case reports or case studies in the medical culture is forgotten. However, reports of clinical cases in the medical press are an important tool in acquiring and understanding new information. Any study of multiple cases must derive from the study of an individual case. The presentation of a case is recommended when the level of uncertainty is high, the theory and direction are obscure and the situations are novel and complex. These criteria are met in our case since we do not know the previous communication of “sighs” by ticagrelor [31].

GPs should always be attentive to opportunities to reflect on their practice, as one of the main methods of learning and professional and personal development. An important role of the daily work of the GPs is to observe the real life in front of the life taken from a “clinical trial”. Thus, the learning that can be achieved from this “not so anecdotal” case, as it may seem, refers us to several more important topics and concepts. Table 1 shows the conclusions of this case, which are important concepts of general medicine.

On the other hand, the repercussion of the case presented in the real world experience does not evidently mean that the prescription of ticagrelor should be discouraged. Although in some patients like the one presented may need an interruption. In any case, definitely, patients should be well informed about adverse effects to drugs and doctors think about them.

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