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Research article

Intensive Pharmacovigilance study, carried out in mexican population with a history of acute myocardial infarction or angina treated with clopidogrel, generic drug, for secondary prophylaxis

Arcelia H A*, Eduardo H A J, Helios V G, Ricardo Z, José Luis R S

Fray Bernardino de Sahagún, Mirador del Punhuato, Morelia, Michoacán, Mexico, North America

ABSTRACT

The results obtained from an intensive pharmacovigilance, phase IV, single-center study, with an oral treatment for secondary prophylaxis of acute myocardial infarction or angina with clopidogrel, generic drug, in Mexican population, at a daily dose of 75 mg, alone or associated with acetylsalicylic acid, are described. A total of 60 patients were admitted; 10 patients were discontinued from the study due to different causes. The patients had, at least, 2 comorbidities in addition to heart disease. Among the most important history were obesity 40% and overweight 41.6%; the age range (tenths) with the greatest number of participants was 51 to 60 years with 25 patients, which represents 41.6%. A total of 247 adverse events were reported (57 patients had adverse events) of which 39 (15.7%) events were heart events, 32 (12.9%) vascular events; 14 (5.7%) events were serious, 9 (3.6%) of the serious events were heart events, 2 (0.8%) vascular events and 3 (1.2%) lithiasis; Of the 24 (9.7%) events, than were classified with a possible causal relation with clopidogrel, 1 (0.4%) was classified as serious. All the other events were non-serious. It was, therefore, concluded that generic clopidogrel is safe, and risk possibility should continue to be monitored for the type of disease that patients suffer and that may have a fatal outcome

Keywords: Pharmacovigilance, generic drugs, adverse event, Med-DRA method

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Correspondence: Arcelia H A * ✉ arcelia.herrera@cecype.com

Head of Pharmacovigilance, Fray Bernardino de Sahagún, Frac. Mirador del Punhuato, Morelia, Michoacán, Mexico, North America

INTRODUCTION

In Mexico, generic drugs must obtain a marketing authorization through a bioequivalence study with the innovative product, which is granted by the National Regulatory Agency, the Federal Commission for the Protection against Sanitary Risk (COFEPRIS). The renewal of the marketing authorization must be done every 5 years [1]. Among some of the requirements requested for this renewal is the latest Periodic Safety Report. This Periodic Safety Report (PSR) is annual or tri annual and should indicate suspected adverse drug reactions (SADR), which were reported during the last period. If this PSR has zero SADR or zero Adverse Events, COFEPRIS, through the National Pharmacovigilance Center (CNFV), does not consider the drug to be safe but that the pharmacovigilance activities of the pharmaceutical laboratory are improper [2].

According to the Pharmacovigilance Newsletter, 50% of the reports received in Mexico were made by the chemical and pharmaceutical industry (CPI) and 0.3% by health professionals [3]. Only the 0.006% corresponds to reports made by patients. CPI Reports correspond to clinical studies that conform the benefit/risk profile of a new or innovator product, and it is expanded by the outcome of its pharmacovigilance programs at various sites with trained personnel. While with generic drugs, their pharmacovigilance departments receive little or no spontaneous notifications, which are, like in most countries, the most frequent reporting methodology. This low SADR notification level gets the generic drug industry in a dilemma when trying renew its registration or at the moment to implement pharmacovigilance activities with health professionals with little experience to develop “real-world” observational studies as an institutional activity, since they are the main prescribers of generic drugs. Ultra Laboratorios, S.A. de C.V., decided to conduct an intensive pharmacovigilance study with the generic drug clopidogrel, in order to monitor the safety of its drug, without modifying the clinical scheme that patients would carry out in real life.

Methods

The Research Ethics Committee approved this study on

June 23, 2014 (approved under number CEI-080); in turn, the Research Committee approved the study on June 23, 2014 (approved under number CI-080). Both Committees belong to the Research Site: Clínica de Enfermedades Crónicas y de Procedimientos Especiales, S.C., located in Morelia, Michoacán, Mexico, the study was conducted at this site (with protocol code IC1212-12CEC). COFEPRIS approved the study (with number 133300410A0198/2013). The National Pharmacovigilance Center assigned a code to record adverse events starting in 2016 (assigned code CNFV/FI/00206/2016).

Study Design

Intensive, phase IV, post-marketing, open-label, non-randomized, observational, descriptive, prospective, longitudinal, single-site pharmacovigilance study in patients with a recent history of acute myocardial infarction or unstable angina and having prophylactic treatment with oral clopidogrel at a daily dose of 75 mg.

The patients were reviewed and monitored by a team that included a cardiologist, general practitioners, nursing staff, pharmacy staff, site coordinator, pharmacovigilance officer. All staff participating in the study were trained in Good Clinical Practices [4]. The reports of adverse events (AEs), suspected adverse drug reactions (SADR) or adverse drug reactions (ADRs) were conducted in accordance with the provisions of current NOM-220-SSA. EA were classified according [5-6] to Table 1.

The Naranjo algorithm was used to standardize the causal relation between SADR and clopidogrel. To evaluate treatment adherence, the Morisky Scale [7] and the Nottingham Health Profile were used [9].

DEFINITION	ASSESSMENT CRITERIA
Serious	Results in death. Is life-threatening. Requires in-patient hospitalization or prolongation of existing Hospitalization. Results in persistent or significant disability/incapacity. Is a congenital anomaly/birth defect. Medically important.
Non serious	Does not meet the above criteria.
Causality term	Certain Event or laboratory test abnormality, with plausible time relationship to drug intake. Cannot be explained by disease or other drugs. Response to withdrawal plausible (pharmacologically, pathologically) Event definitive pharmacologically or phenomenologically (i.e., an objective and specific medical disorder or a recognized pharmacological phenomenon). Rechallenge satisfactorily, if necessary. Probable/likely Event or laboratory test abnormality, with reasonable time relationship to drug intake. Unlikely to be attributed to disease or other drugs. Response to withdrawal clinically reasonable. Rechallenge not required. Possible Event or laboratory test abnormality, with reasonable time relationship to drug intake. Could also be explained by concomitant disease or other drugs. Information on drug withdrawal may be lacking or unclear. Unlikely Event or laboratory test abnormality. With time to drug intake that makes a relationship improbable (but not impossible). Disease or other drugs provide plausible explanations. Conditional / Unclassified Event or laboratory test abnormality. More data for proper assessment needed or additional data under examination. Unassessable / Unclassifiable Report suggesting an adverse reaction. Cannot be judged because information is insufficient or contradictory. Data cannot be supplemented or verified.

Data Collection

The study began in January 2015 and ended in January 2018. Following the signature of the Informed Consent Form, patients were summoned monthly for 12 months, in order to provide them with 75 mg clopidogrel tablets (Ultra Laboratories) and, for those who required it, with acetyl salicylic acid (ASA), the dose they had indicated prior to the start of the study. The first provision of clopidogrel was considered as the first appointment; each patient who completed the study was given clopidogrel 12 times and was summoned one month after the last drug provision, in order to collect data on adverse events and to discharge them from the study. Between appointments, patients could make phone calls to report any eventuality. During each appointment, the handwritten notes in the source document were collected, they were filled with the clinical status and the presence or absence of adverse events that could have occurred to patients during that month; additionally, the patients returned the leftover medication, in order to assess adherence to treatment, and they were given more medicine. During visits 01, 04, 07 and 12, laboratory tests and electrocardiogram were taken, Nottingham and Morisky questionnaire was applied and subjects were evaluated by the cardiologist physician [10].

Statistical Analysis

All data obtained were analyzed using Microsoft ® Excel ® 2013 (15.0.4420.1017) MSO (15.0.4420.1017) software. Average, maximum and minimum values, standard deviation (SD), and coefficient of variation (CV) were used; Nottingham and Morisky questionnaires, as well as averages, were obtained by appointment, as the number of patients varied at different visits. Patients who consumed at least one dose of the drug were taken into account for the statistical analysis.

Measured Study Variables

The MedDRA version 21.0 dictionary was used for the clinical classification of SADR, using the System Organ Class (SOC) and the preferred term (PT). According to version 21.0 of the MedDRA dictionary, which is divided into 27 main hierarchies or System Organ Classes called SOC (even in the Spanish version), a lower hierarchy, the Preferred Term, was used as a sign or symptom. For the classification of the seriousness of adverse events and causality, the classification indicated in Table 1 was applied. For treatment adherence, the Nottingham and Morisky questionnaire was applied as described in the protocol[11].

All patients included in the study signed the Informed Consent Form before any questionnaire or measures were taken; all of them met the inclusion criteria specified in the protocol and none of them showed non-inclusion criteria.

Patient demographics can be seen in Table 2, which lists

age, weight, height, and body mass index or BMI. Regarding participant's gender, 21 (35%) were female and 39 (65%) were male; the most affected age range was between 51 and 60 years with 25 (41.6%) patients, of whom 19 were males and 6 were females.

Table 2. Demographic data, concomitant medications, and comorbidities

DATA	AGE	WEIGH	SIZE	BMI*
Average	58.2	77.35	1.62	29.49
SD*	9.98	13.12	0.09	4.99
CV%*	17.15	16.96	5.72	16.91
Maximum	80	107.5	1.79	42.6
Minimum	38	52.9	1.42	20.5
Concomitant medications	Metoprolol	Furosemide	Metformin	Allopurinol
	Losartan	Enalapril	Glibenclamide	Bezafibrate
	Hydrochlorothiazide	Amlodipine	Atrorvastatine	Levothyroxine
	Telmisartan	Isosorbide	Insulin	Digoxin
COMORBIDITIES			TOTAL (60)	PERCENTAGE
Alcoholism			18	30
Type II Diabetes			20	33.3
Systemic Arterial Hypertension			40	66.6
Smoking			32	53.3
Obesity			24	40
Overweight			25	41.6
Dyslipidemia			15	25

*BMI: Body mass index (kg/m^2)
*SD: Standard Deviation
*CV: Coefficient of Variation

This table refers to the history that patients reported upon admission to the study. Demographic data are given for age, weight, height and BMI, the concomitant medications that patients used for their comorbidities and comorbidities with the total number of patients with comorbidity and percentage.

The admission diagnoses of the patients included were:

1. Acute ST-elevation myocardial infarction, 21 (35%) patients.
2. Acute non-ST-elevation myocardial infarction, 9 (15%) patients.
3. Unstable angina with electrocardiographic changes, 25 (42%) patients.
4. Unstable angina without electrocardiographic changes, 5 (8%) patients.

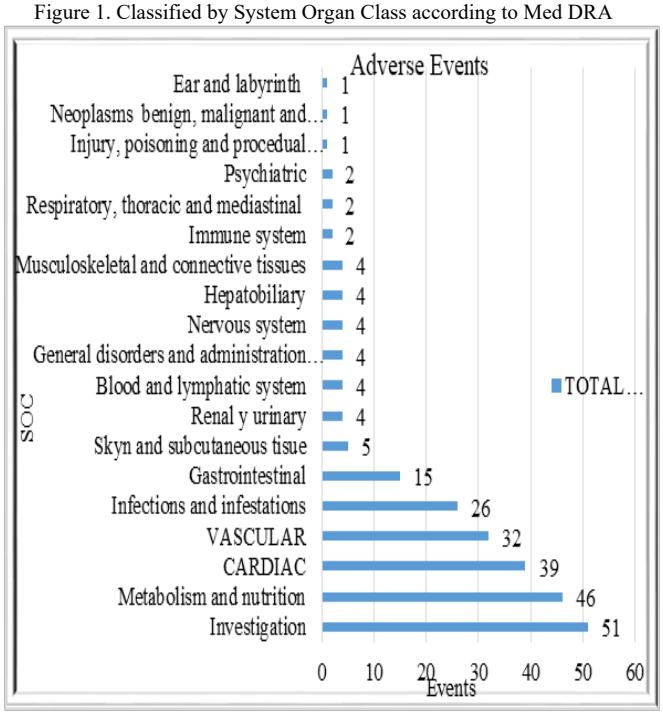
The time since the patients were diagnosed with heart disease was from 1 to 24 months, with an average of 7 months. Among the most important concomitant diseases found (see Table 2) were: alcoholism, type II diabetes, systemic arterial hypertension, smoking, obesity, overweight and dyslipidemia, most patients had at least two comorbidities. The concomitant medications used for the treatment of comorbidities and the number of patients using them were: metoprolol (23), losartan (19), hydrochlorothiazide (6), furosemide (5), telmisartan (5), enalapril (9), isosorbide (20), metformin (16), glibenclamide (8), insulin (3), allopurinol (4), bezafibrate (7), atorvastatin (42), amlodipine (5).

Regarding the treatment reported by patients at baseline, 39 (65%) patients were taking clopidogrel and 21 (35%) clopidogrel + ASA.

RESULT

60 patients were included in the study, 50 of them completed the 12 visits specified by the protocol. The causes for discontinuation from the study of the 10 patients who did not complete the study were than 6 patients withdrawn consent to participate in the study (for personal reasons, including address change), 2 patients were considered loss to follow-up, 1 patient was withdrawn due to a serious adverse event while and 1 was due to a fatal serious adverse event.

Figure 1. Classified by System Organ Class according to Med DRA



A total of 247 adverse events, related and unrelated to clopidogrel, were recorded during the study, 57 subjects had adverse events. Of the 27 system organ classes, or groups and systems, called SOC, according to version 21.0 of the MedDRA dictionary,[11] there were events registered in 19 SOCs during the study, as can be seen in Figure 1

In vascular SOC (see Table 4), to define the clinical safety of the drug, there are suspected adverse drug reactions that may be causality-related with clopidogrel, since it inhibits platelet aggregation and can cause bleeding. In this SOC, 32 (12.9%) events were reported, of which 2 were classified as serious; one serious adverse event was hematuria; this patient had a history of prostatic hypertrophy. The presence of bleeding in the urinary tract caused him anguish, which forced him to carry out hospital monitoring, without requiring treatment, and to be classified as serious following the event, the patient withdrew consent, deciding not to continue in the study. The other event occurred in a patient who presented an aortic aneurysm within few days of starting study participation. The aneurysm required surgery for rupture, with fatal outcome of these two serious events, only hematuria was found to have a possible causality relation with clopidogrel, even though the patient had a history of urology that could also cause bleeding through the urinary tract.

Table 3. Cardiac Adverse Even

CARDIAC DISORDERS	FREQUENCY	SERIOUSNESS
	39 (15.80%)	
Angina pectoris	1 (0.40%)	Serious
Angina pectoris	4 (1.62%)	Non-serious
Angina pectoris unstable	2 (0.80%)	Serious
Angina pectoris with cardiac therapeutic procedures	1 (0.40%)	Serious
Anginal pain	1 (0.40%)	Serious
Arrhythmia	1 (0.40%)	Serious
Ventricular Arrhythmia	1 (0.40%)	Non-serious
Atrioventricular block	1 (0.40%)	Non-serious
Bradycardia	4 (1.62%)	Non-serious
Chest pain	16 (6.48%)	Non-serious
Ventricular extrasystoles	1 (0.40%)	Non-serious
Lower myocardial infarction	1 (0.40%)	Serious
Myocardial ischemia (Coronary stent placement)	1 (0.40%)	Serious
Palpitations	1 (0.40%)	Non-serious
Syncope	1 (0.40%)	Serious
Tachycardia	2 (0.80%)	Non-serious

Table 4. Vascular Adverse Events

VASCULAR DISORDERS	TOTAL 32 (12.95%)	SERIOUSNESS
Epistaxis	1 (0.40 %)	Non-serious
Ecchymosis	22 (8.90 %)	Non-serious
Gingival bleeding	1 (0.40 %)	Non-serious
Subconjunctival hemorrhage	3 (1.21 %)	Non-serious
Aortic aneurysm	1 (0.40 %)	Serious
Rectal Bleeding	1 (0.40 %)	Non-serious
Hematuria	1 (0.40 %)	Serious
Hematemesis	1 (0.40 %)	Non-serious
Vaginal bleeding	1 (0.40 %)	Non-serious

The most frequent of vascular adverse events was classified in PT as ecchymosis with 22 events, all classified as non-serious. Regarding causality, 24 (9.7%) vascular adverse events were considered to be related to clopidogrel. Regarding the remaining 17 categories that concentrated adverse events 13 of them grouped from 1 to 5 adverse events. The classification corresponding to gastrointestinal disorders with 15 (4.9%) events, included 5 patients with diarrhea, 2 with nausea, 2 with pain, and 1 with heartburn. In the Infections and infestations SOC with 26 (10.5%) events, which is a SOC considered as primary, according to MedDRA classification,[11] even if the infection is in a given organ, preference is given to this SOC, and it is common for anyone to have an infectious process in the course of 1 year. All of these events were considered as non-serious and without any association with the Investigational Medical Product. All of these events were classified as non-serious and unrelated to clopidogrel.

In the metabolism and nutrition disorders SOC, 46 (19%) events were reported, of which 21 (9%) correspond to the Preferred Term (PT) hypertriglyceridemia and 11(4%) to PT hypercholesterolemia, which are events related to the concomitant diseases of the patients; all of them were classified as non-serious. It is important to note that 42 patients were taking atorvastatin since their admission. In the investigation SOC with 51 (21%) events, the laboratory results are situated, evaluated on 4 occasions; outliers results were reported in this SOC; events were considered as adverse due to laboratory outliers not by patient or date. All events were classified as non-serious and most of them were not clinically relevant to the study.

Causality

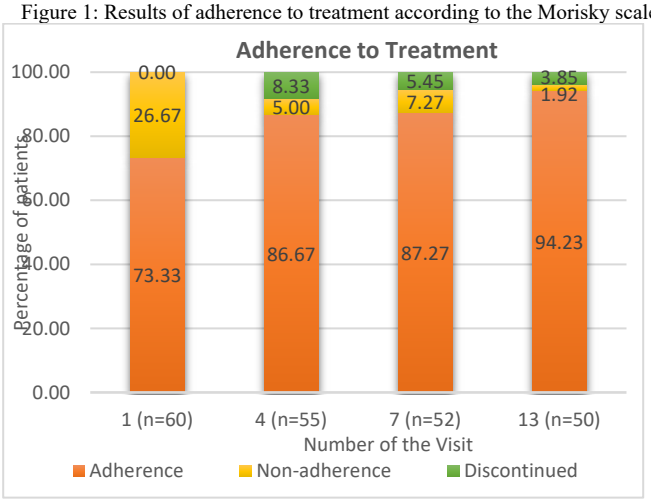
The causal relation was performed only for clopidogrel, using the Naranjo algorithm of the 247 events recorded during the study, 24 (9.7%) were considered as probably related to clopidogrel. All the events classified as possible corresponded to the vascular disorders SOC; 1 event was classified as serious, the one corresponding to PT hematuria. This patient was diagnosed with cysto urethritis due to prostatic hypertrophy; the patient was taking clopidogrel + ASA, which could increase bleeding probability.

Treatment Adherence

As a result of the application of the Morisky scale, to assess patient treatment adherence throughout the study, it was observed (see Figure 2), in the first application of the scale, with the participation of the 60 patients, an adherence of 73.3% and, in the last visit, with a participation of 50 patients (those who completed the study), an adherence of 94.23%, non-adherence of 1.92% and 3.85% discontinuations from the study, which means that, during the course of one year of treatment, the patient's adherence to clopidogrel improved to a point were almost a total adherence can be observed at the end of the study. One advantage of this type of study is that it can improve physician-patient relationship and the health care quality, increasing the adherence in the process.

In figure 2 shows the adherence to treatment of the patients during each of the four visits in which this scale was applied. Where n is the number of patients that continued in the study. The scale shows the percentage of patients who adhered to the treatment; those who adhered, those with no-adherence and those that were discontinued from the study for various reasons. 60 patients were admitted and 50 concluded.

Figure 1: Results of adherence to treatment according to the Morisky scale



The Nottingham Health Profile, as well as the Morisky Scale, was applied according to the protocol on 4 occasions. In this scale,

zero represents the best score and 100 the worst. According to Figure 3, a score of 26 can be observed in the first application of the health profile and a score of 15 during the last visit. Although a slight improvement can be perceived, there was, actually, a great variability in results throughout all visits.

All serious adverse events that occurred during the study were reported to the Institutional Committees, the National Pharmacovigilance Center (NPVC) and the sponsor, within 15 days of being aware of the serious event. In addition, five semi-annual reports were made to the NPVC. Two final reports of the study were made to the Institutional Committees.

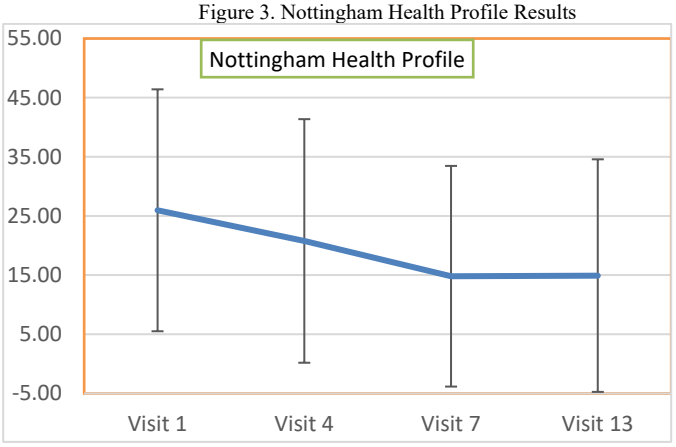
DISCUSSION

The demographic characteristics of patients, as well as the type of comorbidities and concomitant medications (see Table 2), are very similar to that reported in literature with similar studies, such as the CURE (The Clopidogrel in Unstable Angina to Prevent Recurrent Event) study, which was taken as a reference for drafting the protocol of this study,[13, 14] the most relevant difference in demographic data would be the high percentage of patients with obesity and overweight according with table 2.

In relation to the occurrence of cardiac events, 15% of the patients had a second event. Those patients reported 39 cardiac adverse events, but only 3.6% of the total adverse events were considered serious. None of these patients had a fatal outcome and they all continued the treatment. The causes of cardiac adverse events can be multifactorial, including possible ineffectiveness, comorbidities, lack of adherence to diet, or other concomitant medications, or even to genetic factors in patients. However, none of these events was classified as causally related to clopidogrel. 32 vascular events occurred during the study, from these events it can be considered that a patient had higher bleeding. He was a 69 year male patient, with a history of obesity since childhood, hypertensive, diabetic, intensely smoking since the age of 20, with BMI 35, diagnosed with unstable angina with ST-segment elevation, with 3 months of evolution, treated with 50 mg losartan per day, 850 mg metformin per day, and 75 mg clopidogrel per day. Two days after his first visit, family members reported that the patient had moderate to severe colicky abdominal pain, accompanied by nausea and vomiting, and was hospitalized, diagnosing a rupture of right common iliac artery aneurysm. One day later, he underwent surgery and died during the surgical procedure. The diagnosis was subsequently confirmed when the family members provided a copy of the tomography result; the event was classified with an improbable causality due to the short time elapsed since he was admitted to the study. This vascular event, corresponding to a ruptured aneurysm, cannot be considered to have been caused by clopidogrel, nor was it considered a doubtful causality, since the formation of the aneurysm or its rupture could not have been caused by the Investigational Medical Product.

With regard to the health profile (see Figure 3), there seems to be a slight improvement, in general terms 50 points were not exceeded, there were patients who qualified at the first visit with 87. This may be because patients are aware that the disease they suffer is chronic and that they may improve and decrease risks with adherence to treatment or treatments and adherence to diet, which is the most difficult part to control. But they have the knowledge that there will be no cure for their disease.

Figure 3. Nottingham Health Profile Results



The score on this scale ranges from 0 to 100, where 0 represents the maximum well-being and 100 the worst perceived state of health.

As for the difference in how the benefit/risk profile is proved by the innovator and generic drugs, in Mexico the National Regulatory Agency (COFEPRIS) publishes each year a list of drugs with which the generic drug requires comparison. The innovator indicated in this specific case carried out all the studies required by Regulatory Agencies recognized by COFEPRIS, such as the carcinogenesis preclinical, reproductive toxicity, single-dose, repeated-dose toxicology studies; it also carried out clinical studies, in which it demonstrated efficacy and safety, and the risk/benefit profile is supported by controlled clinical studies, for the adverse events reported during these studies. The generic drug should then support benefit/risk through the spontaneous notifications presented in the Periodic Safety Reports and, in the event of limited notifications, a real-world intensive Pharmacovigilance observational study may modify or continue with the same safety profile. In this case, according to the studies presented by the innovator, in which fatal infarction was reduced by 9.8% as a secondary prevention and, in terms of safety, they occurred in 2.16% of the fatal bleeding patients and 11.62% bleeding that did not require discontinuation of treatment.[16] In this study, 3.6% of cardiac events with no fatal outcome occurred; in terms of safety, 9.7% of the events were

causality-related with clopidogrel and these were ecchymosis, which can be considered as bleeding that did not require discontinuation of treatment, so the benefit/risk profile demonstrated by the innovator was not modified.

This study also provides the quality of the generic product, previously demonstrated during the conduction of the bioequivalence study with which the Marketing Authorization of the medical product was obtained, as well as compliance with good laboratory practices, which it complies with and demonstrates when audited by the Health Authority, which cannot always review, nor can it review the total of lots distributed in the market. A study of this type may also highlight the quality of the generic drug if the benefit/risk profile is appropriate. This would be so if there were any deviations from inefficacy or serious adverse events more frequent than the ones reported, or the presence of an unexpected adverse event would be an alarm on product quality. This study provides the evidence of the benefit/risk profile of the product. But, by performing a real-life study and maintaining its profile similar to the innovator, the quality of the generic is demonstrated.

It is important to describe what does it means to open a private site for a Pharmacovigilance study outside a public health institution. It does not only represents having an area to perform a common medical activity; it is necessary to have continuously trained personnel with a robust quality management system, so that its processes can carried out according with the provisions of a protocol with specific characteristics in pharmacy, in documentation, in equipment, for it to be monitored in order to ensure the safety of the patient and comply with the health framework. It also represents to search for specialists interested in the research area, who are able to comply with good clinical practices, giving timely follow-up to the observations made by the monitors, and, the most delicate thing, to look for and keep the patients throughout the study.

One of the main complications of a private institution, conducting pharmacovigilance studies, is the approach to specialists or prescribers, which may be due to multiple causes. One of the main reasons is that, at the school level, there is not a subject in which research and proper documentation of the clinical records are carried out, also, it might be than asking prescribers to participate in a study could be considered by them as an intrusion into their private practice or a competition. There are also economic and time factors.

The study had a duration of 13 months and it took 3 years to complete it, due to the difficulty of completing the initial sample size. The patients admitted in the study continued their visits with the specialist who were in charge of their care, either in private practice or at the institutional level, so, when the study was completed, the patient continued its usual consultations.

Having the adequate documentation of adverse events, without prescribing physicians considering it as a failure to apply their knowledge or therapy in Mexico, it is one of the greatest improvements that could be made in the health education sector. If all of the students participate, it can be achieved to educate the patient not only in reporting but in properly understanding its prescriptions and, what is more important, in a proper adherence to treatment.

CONCLUSION

The importance of multidisciplinary teams in pharmacovigilance is essential in order to achieve notifications of a proper quality but it isn't only at the level of the large pharmaceutical industries that are currently using artificial intelligence that includes photovoltaic energy as a tool in pharmacovigilance because the small pharmaceutical companies that produce generic medical products can work together in pharmacovigilance in order to train teams; they can conduct studies like this one and maintain permanent sentinel sites to train patients to perform spontaneous reports; or conduct educational campaigns in health-related schools, in such a way that the members of an entire generation, upon finishing their studies, would have the required knowledge, practice and interest because they would know the importance of making spontaneous reports, so, if they carry out joint activities, they can promote joint risk minimization activities and obtain better results with reports.

Comparing the results of this real-life study with the controlled studies performed by the innovator, it can be concluded that generic clopidogrel is safe because its benefit/risk profile was not modified in comparison to the innovator medical product, thus, it maintains its quality. Patients may have a low but possible risk that should be followed up, mainly, because of the patient's type of disease and comorbidities.

This study sets a precedent for the pharmaceutical industry in Mexico, because it leaves the experience that performing a real-life post-marketing pharmacovigilance study represents not only having a pharmacovigilance team trained to properly document the adverse events and the study results, but the most important thing is that it demonstrates the generic drug's quality and provides evidence about the its benefit/risk profile attested by the results of the performed study.

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Disclosures

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from the sponsoring laboratory. No advice was received from any government agency for the drafting of the article.

Data availability statement

The data in this manuscript will be available in compliance with the confidentiality of the participating subjects and with the confidentiality agreements of the sponsor.

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