Study Protocol

Drugs associated with Spontaneous Coronary Artery Dissection: a WHO pharmacovigilance database disproportionality analysis

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March 23, 2022

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Introduction

Spontaneous coronary artery dissection (SCAD), defined as a separation of the layers of an epicardial coronary artery wall by intramural hemorrhage (with or without intimal tear) causes approximately 1% of myocardial infarctions (MI), but accounts for about 25% of the MI in women younger than 50 years [1]. SCAD occurs predominantly in young women (sex ratio of 9) with few or no cardiovascular risk factors and is not associated with atherosclerosis. The SCAD cause is unknown but several risk factors have been identified: predisposing arteriopathies (such as fibromuscular dysplasia, pregnancy, connective tissue disorder, coronary spasm) and precipitating stress factors (such as emotional or physical stress, delivery, Valsalva maneuvers, illegal drugs as cocaine [2] and amphetamines, intense hormonal therapy) [4]. Up to 72% of patients with SCAD are diagnosed with fibromuscular dysplasia (FMD) [3].

Beyond hormonal therapy and amphetaminic-like drugs several cases reports hypothesized a role of various compounds in triggering SCAD (topiramate [5], oestrogens [6, 7], HCG [8], leuprorelin [9]).Moreover, one recent disproportionality analysis using the WHO pharmacovigilance database showed a significant pharmacovigilance signal for triptans and SCAD [4]. However, no study has been carried out on large scale pharmacovigilance databasesto comprehensively assess the cases and the disproportionality signals for all drugs.

The aim of this study is to assess if other drugs are associated with SCAD using a case non case design in the WHO pharmacovigilance database, Vigibase.

Methods

Data source

We will perform a case non-case study using Vigibase®, the World Health Organization Global Individual Case Safety Reports (ICSRs) database which includes more than 29 million reports (at January 2022) forwarded to the WHO Uppsala Monitoring Center by national pharmacovigilance systems from over 130 countries around the world since 1967. ICSRs are spontaneously generated accounts of adverse drug reactions describing a suspected causative agent, as reported by health professionals, consumers, or the drug manufacturers.

Study population

We will include all ICSRs registered until December 31, 2021, from patients with age > 18 years old, and with sex known. Given that Percutaneous coronary intervention (PCI) is the main cause of iatrogenic coronary artery dissection, we will exclude all ICSRs from drugs that may be used during PCI such as aspirin, PZY12 inhibitors, GpIIb/IIIa inhibitors and anticoagulant therapies (VKAs, heparins, NOACs, fibrinolytic therapies). We finally exclude ICSRs from COVID 19 vaccines because of potential over reporting.

Case and non-case definition

Cases were all ICSR from the study population defined by the MedDRA Preferred Term (PT) "coronary artery dissection".

Non-cases will be all other reports from the study population recorded in VigiBase ® during the same period of interest.

Outcomes

The main outcome will be reporting odds ratio (ROR) for each drug of interest (defined as at least 3 ICSR). The reporting odds ratio (ROR) for each drug of interest is the reporting odds of SCAD among exposed patients, over the reporting odds of SCAD among non-exposed patients. 95% lower-end credibility interval for the ROR (ROR025) is deemed significant when > 1.

Exposure definition

For both cases and non-cases, we will identify patients from the study population exposed to drugs registered in the database for at least 1 ICSR of coronary artery dissection.

Data analysis

Descriptive statistics will be used to compare characteristics between reports. Using a case/non-case design, we will estimate ROR for each drug of interest. Moreover, we will conduct sensitivity analyses to assess the robustness of the signals. We will restrict analysis to reports declared by a healthcare physician. To take in account the potential confusion bias induced by the population characteristics exposed to a given drug we will modify the comparator group by using all cases reported with drugs belonging to the corresponding ATC class 3 level.

Data extraction

Data extraction of reports (ICSRs) of interest was done in February 2022.

Ethics

As all data from VigiBase® were deidentified, patient informed consent will be not necessary.

Amendments and deviations

Any future amendments or deviations will be recorded here.

References

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