SFDA SAFETY SIGNAL

"A signal is defined by the SFDA as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature"

24-11-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Azithromycin and the Risk of Ventricular fibrillation

The Saudi Food and Drug Authority (SFDA) recommends all health care professionals to be aware of the safety signal of ***Ventricular fibrillation associated*** *with the use of* ***Azithromycin****. The signal has been originated as a result of routine pharmacovigilance monitoring activities.*

Introduction

Azithromycin bind to 23S rRNA of 50S ribosomal subunit and prevents protein synthesis by inhibiting the assembly of the 50S ribosomal subunit. It is indicated to treat community-acquired pneumonia and pelvic inflammatory disease caused by susceptible organisms, including Legionella pneumophila, in patients indicated for IV therapy [1]. Ventricular fibrillation (VF) is an ineffective ventricular contractions or fast shivering of the ventricular walls that prevents them from pumping the blood properly which is a life-threatening cardiac rhythms [2]. The aim of this review is to evaluate the risk of Ventricular fibrillation associated with the use of Azithromycin and to suggest regulatory recommendations if required.

Methodology

Signal Detection team at the National Pharmacovigilance Center (NPC) of Saudi Food and Drug Authority (SFDA) performed a comprehensive signal review using its national database as well as the World Health Organization (WHO) database (VigiBase), to retrieve related information for assessing the causality between Azithromycin and the Risk of Ventricular fibrillation [3]. We used the WHO-Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [4].

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 75 global ICSRs as of February 2021 [3]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.5 and above (25 ICSRs); the value 1.0 indicated

the highest score for best-written ICSRs. Among the reviewed cases, about half of them provides supportive association (2 probable, and 9 possible cases).

Data Mining: The disproportionality of the observed and the expected reporting rate for drug/adverse drug reaction pair is estimated using information component (IC), a tool developed by WHO-UMC to measure the reporting ratio. Positive IC reflects higher statistical association while negative values indicates less statistical association. The results of (IC= 1.4) revealed a positive statistical association for the drug/ADR combination, which means "Ventricular fibrillation " with the use of "azithromycin" have been observed more than expected when compared to other medications available in WHO database [3].

Literature A search in literature was conducted to find relevant studies however; the only results found are describing the risk of ventricular arrhythmia, a condition with slightly less severity than ventricular fibrillation:

In a case–control study within a cohort of new antibiotic users identified from a network of 7 population-based health care databases in 5 countries between 1997 and 2010. There were 14,040,688 new antibiotic users who met the inclusion criteria. Therefore, Ventricular arrhythmia established in 12,874. Azithromycin use was associated with an increased risk of ventricular arrhythmia when compare to amoxicillin [5].

In a case report for a 24-year-old black female with no medical history that was treated with azithromycin for URTI for 5 days. After 24 hours of discontinuing azithromycin, she experienced some symptoms of syncope that she went to the emergency department to seek care. Her ECG upon admission was normal then she developed Ventricular tachycardia (VT) with a normal QT interval when syncope developed. When she stayed azithromycin free, her ECG and her symptoms resolved over 3 days [6].

Another study aimed to detect signals of cardiac disorders associated with azithromycin from Health Canada database. The authors found that, Mitral valve disease was reported in 3 out of 105 pediatrics (3%) and 3 out of 439 (1%) of the adult population among of all cardiac related ADRs [7].

Conclusion

The weighted cumulative evidences identified from the reported cases, data mining and literature are sufficient to support a causal association between Azithromycin and the risk of Ventricular fibrillation. Health regulators and health care professionals must be aware of this potential risk and it is advisable to monitor any signs or symptoms in treated patients.

Report Adverse Drug Events (ADRs) to the SFDA

The SFDA urges both healthcare professionals and patients to continue reporting adverse drug reactions (ADRs) resulted from using any medications to the SFDA either online, by regular mail or by fax, using the following contact information:

National Pharmacovigilance Center (NPC)
Saudi Food and Drug Authority-Drug sector
4904 northern ring branch rd
Hittin District
Riyadh 13513 – 7148
Kingdom of Saudi Arabia
Toll free number: 19999
Email: NPC.Drug@sfda.gov.sa

References:

1. Pharmacia Upjohn Company LLC. Saudi Summary of Product Characteristics (SPC) of Azithromycin (ZITHROMAX) ®; (retrieved from EURS). [Accessed 2/4/2021]
2. Ventricular Fibrillation and Pulseless Ventricular Tachycardia. Available at: https://nhcps.com/lesson/acls-cases-ventricular-fibrillation-pulseless-ventricular-tachycardia/ [Accessed on: 2/11/2021].
3. Uppsala Monitoring Center (UMC) (2021), Vigilyze database; Available at: https://vigilyze.who-umc.org [Accessed 2/8/2021].
4. Uppsala Monitoring Center (UMC) (2021), The use of the WHO-UMC system for standardized case causality assessment; Available at https://www.who.int/medicines/areas/quality_safety/safety_efficacy/WHOcausality_assessment.pdf?ua=1 [Accessed 2/8/2021].
5. Trifirò G, de Ridder M, Sultana J, et al. Use of azithromycin and risk of ventricular arrhythmia. CMAJ. 2017;189(15):E560-E568. doi:10.1503/cmaj.160355. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5392117/ [Accessed 2/11/2021].
6. Azithromycin Causes a Novel Proarrhythmic Syndrome. Available at: https://www.ahajournals.org/doi/10.1161/circep.115.003560 [Accessed 2/11/2021].
7. International Journal of Pharmacy and Pharmaceutical Sciences. Available at: https://www.researchgate.net/publication/317366190_SAFETY_SIGNAL_DETECTION_OF_CARDIAC_DISORDERS_ADVERSE_DRUG_EVENTS_FOR_AZITHROMYCIN_IN_PEDIATRIC_POPULATION_USING_HEALTH_CANADA_ADVERSE_EVENT_REPORTING_SYSTEM_DATABASE [Accessed 2/8/2021].