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"

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Saudi Food and Drug Authority (SFDA) – Safety Signal of Donepezil and the Risk of QT prolongation

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

Introduction Donepezil is a reversible inhibitor of acetylcholinesterase specifically in the brain. It is indicated mainly for symptomatic treatment of mild to moderately severe Alzheimer's dementia [1]. The QT interval is the start of the Q wave to the end of the T wave time, the time spent for ventricular depolarization and repolarization, that QT interval would be considered prolonged if it was > 440ms in men and > 460ms in women (> 500 is associated with increased risk of torsades de pointe) [2]. The aim of this review is to evaluate the risk of QT prolongation associated with the use of Donepezil 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 Donepezil and the Risk of QT prolongation [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 132 global ICSRs as of December 20, 2020 [3]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.63 and above (30 ICSRs); the value 1.0 indicated the highest score for best-written ICSRs. Among the reviewed cases, more than half of them provides supportive association (7 probable and 14 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, considering the null value equal to zero. The results of (IC= 3.1) revealed a positive statistical association for the drug/ADR combination, which means "QT prolongation" with the use of "Donepezil " have been observed noticeably more than expected when compared to other medications available in WHO database [3].

Literature: Multiple evidences have been found during the literature search, all were suggestive for the association between drug and the adverse event:

In a case report for a 26-year-old African American female was admitted to the inpatient psychiatric hospital .Two normal baseline electrocardiograms (EKGs) were obtained, but after several weeks, of donepezil, a two follow-up EKG tests were done and showed a prolonged QTc of 463 ms and 528 ms. As a result, donepezil was discontinued completely, leading to normalization of the QTc interval. [5].

The article have also summarized other available studies that measures ECG changes in donepezil users. As a result, most of them showed QT prolongation following the use of donepezil [5].

A class effect study evaluated a total of 13 case reports that were 10 cases for donepezil, 2 cases for galantamine and 1 cases for rivastigmine use and its relationship with (QTc) prolongation. Five cases with donepezil exhibited Torsades de Pointes (TdP), but TdP was not reported in the cases with galantamine and rivastigmine. The use of a QT heart rate nomogram suggested a risk with donepezil compared with the other two drugs. Also, the Naranjo causality scale suggested probable or possible causation for all donepezil cases [6].

Conclusion

The weighted cumulative evidences identified from causality assessment of the reported cases, data mining and literature are sufficient to support a causal association between Donepezil and the risk of QT prolongation. Health regulators and health care professionals must be aware for this potential risk and shall 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:

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2. Ed Burns, QT Interval. Nov 3, 2020 Retrieved from https://litfl.com/qt-interval-ecg-library/ [Accessed 12/22/2020].
3. Uppsala Monitoring Center (UMC) (2020), Vigilyze database; Available at: https://vigilyze.who-umc.org/ [Accessed 9/21/2020]
4. Uppsala Monitoring Center (UMC) (2020), 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 23/7/2020].

5. Vogel SM, Mican LM, Smith TL. Donepezil-induced QTc prolongation: A case report. Ment Health Clin. 2019;9(3):128-132. Published 2019 May 10. doi:10.9740/mhc.2019.05.128 Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6513057/ [Accessed 12/26/2020]
6. SAGE journal. Retrieved from https://journals.sagepub.com/doi/full/10.1177/2042098620942416 [Accessed 12/28/2020].