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"

3-1-2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Amitriptyline and the Risk of Drug Reaction with Eosinophilia and Systemic Symptoms

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

Introduction Amitriptyline hydrochloride is a tricyclic antidepressant with sedative properties inhibits the membrane pump mechanism responsible for the re-uptake of transmitter amines, such as norepinephrine and serotonin, thereby increasing their concentration at the synaptic clefts of the brain [1]. Drug-induced hypersensitivity syndrome or drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome is a life-threatening hypersensitivity reaction [2]. The aim of this review is to evaluate the risk of Drug reaction with eosinophilia and systemic symptoms associated with the use of Amitriptyline 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 Amitriptyline and the Risk of Drug reaction with eosinophilia and systemic symptoms [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 29 global ICSRs as of October 4th 2020 [3]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.8 and above (9 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 (2 probable and 3 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= 0.4) revealed a positive statistical association for the drug/ADR combination, which means "DRESS syndrome" with the use of "Amitriptyline" have been observed more than expected when compared to other medications available in WHO database [3].

Literature: Multiple evidences have been found during the literature search. Two published case-reports of amitriptyline with dress syndrome and one case-report of other medication from the same drug class (tricyclic anti-depressant) associated with the same risk.

A case of 24-year-old woman referred to the emergency department because of erythroderma and fever while taking amitriptyline 25 mg orally twice daily because of mild depression. She has been taking it for three weeks when she noticed a pruritic morbilliform rash on the trunk. Her past medical history was unremarkable. Skin biopsy was remarkable. Five days after amitriptyline withdrawal, the patient was afebrile and skin improved [5].

Another case report for a 28-year-old man developed drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome following treatment with amitriptyline and metoprolol. The drugs were withdrawn, and steroids were initiated that lead to systemic reaction to improve. He was rechallenged with vancomycin and penicillins; accordingly, amitriptyline or metoprolol was implicated as the most likely cause of DRESS syndrome [6].

Another published article aimed to review the DRESS syndrome comprehensively. The authors have mentioned multiple medications triggering for this adverse drug reaction. Amitriptyline and desipramine have been mentioned as part of those causative agents [7].

Additionally, evidence on class effect have also been reported in literature following the administration of other tricyclic antidepressant agent (clomipramine), a case-report of DRESS syndrome with pulmonary involvement published in French language [8].

Conclusion

The weighted cumulative evidences identified from the reported cases, data mining and literature are sufficient to support a causal association between Amitriptyline and the risk of drug reaction with eosinophilia and systemic symptoms. 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:

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