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"

13/1/2021

Saudi Food and Drug Authority (SFDA) – Safety Signal of Theophylline and the Risk of Encephalopathy

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

Introduction Theophylline is structurally classified as a methyl xanthine which has two distinct actions in the airways of patients with reversible obstruction; smooth muscle relaxation and suppression of the response of the airways to stimuli [1]. Theophylline is indicated to treat Bronchial asthma, pulmonary infections with bronchial spastic component [2]. Encephalopathy is a term for any diffuse disease of the brain that alters brain function or structure [3]. The aim of this review is to evaluate the risk of Encephalopathy associated with the use of Theophylline 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 Theophylline and the Risk of Encephalopathy [4]. The team used the WHO- Uppsala Monitoring Centre (UMC) criteria as standard for assessing the causality of the reported cases [5]

Results

Case Review: The number of resulted cases for the combined drug/adverse drug reaction are 56 global ICSRs as of June 21th 2020 [4]. The reviewers have selected and assessed the causality for the well-documented ICSRs with completeness scores of 0.4 and above (8 ICSRs); the value 1.0 indicated the highest score for best-written ICSRs. Among the reviewed cases, half of them provides supportive association (2 probable, and 2 possible cases). Also, there are 2 positive dechallenge.

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= 2.4) revealed a positive statistical association for the drug/ADR combination, which means " Encephalopathy" with the use of "Theophylline " have been observed noticeably more than expected when compared to other medications available in WHO database [4].

Literature: Multiple evidences have been found during the literature search. A published article describing the risk of encephalopathy in two patients following the use of theophylline. A two-year-old male received oral maintenance theophylline therapy and a four-year-old male received intravenous theophylline therapy at the time of seizures. Brain CT scans showed diffuse cortical low-density in the acute period. Follow up CT scans revealed progressive cortical low-density in the subacute period and subsequently reached to the peak in the 10th day and 19th day of illness respectively. The authors considered that the progressive and long-lasting severe cortical edema on brain CT scan is characteristic of theophylline-associated encephalopathy [6]. Another evidence found from a study aimed to provide an overview of adverse drug events associated with asthma medications in children. The authors analyzed the spontaneous reports of European Economic Area database (EudraVigilance) and it revealed that, encephalopathies is potentially associated with theophylline use [7].

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 Theophylline and the risk of Encephalopathy. 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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6. Maegaki, Y., Koeda, T., Kawahara, H., & Takeshita, K. (1993). Two cases of theophylline-associated encephalopathy in childhood: clinical and CT findings. No to hattatsu= Brain and development, 25(3), 277-282.
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