



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”

2-1-2018

Saudi Food and Drug Authority (SFDA) – Safety Signal of QT prolongation Associated with the Use of Diphenhydramine products

The Saudi Food and Drug Authority (SFDA) will request from all marketing authorization holders to update the summary of product characteristics (SPC) and patient information leaflet (PIL) of diphenhydramine to include the risk of QT prolongation/Torsades de points in overdose section.

Diphenhydramine is an antihistamine that reduces the effects of natural chemical histamine in the body. Histamine can produce symptoms of sneezing, itching, watery eyes, and runny nose.

Drug-induced prolongation of the QT interval is a serious type of drug toxicity that may lead to the polymorphic ventricular tachycardia, torsade de pointes and in some circumstances lead to sudden cardiac death.

The SFDA initiated the investigation based on a potential signal originating from foreign regulatory authority. The SFDA reviewed all available evidences related to this safety concern including Individual Case Safety Reports (ICSRs) in World Health Organization (WHO) VigiBase as well as screening of the national database. Although there were no locally reported cases, the WHO database revealed 162 internationally reported cases since 1973. Among the total cases resulted, fourteen patients were recovered after stopping diphenhydramine (positive de-challenge) and two patients have worsened after resuming the medication (positive re-challenge) both outcomes are supporting the association.

In addition, a literature review was conducted to determine the possible association of this signal to diphenhydramine. As a result, four case studies agreed that the incident of QT prolongation/Torsades de points appeared following administration of a toxic doses of diphenhydramine ⁽¹⁻⁴⁾.

The prolongation of the QT interval usually occur due to inhibiting the cardiac repolarization phase by blocking the rectifier potassium current (I_{kr}) (Zehra Husain et al.). Diphenhydramine at higher doses (toxic doses) inhibits the potassium channels, which lead to prolonging the action potential process and predispose torsade de point.

The current Saudi SPC stated that diphenhydramine can cause arrhythmia and ECG changes if overdosed, yet not all kind of arrhythmias could result in QT prolongation/Torsades de points and not all ECG changes required same management.

The SFDA investigation concluded that the current available evidence suggests a probable association between diphenhydramine overdose and QT prolongation/Torsades de points. The SFDA will continue closely monitoring this event and will update all concerned healthcare providers upon availability of new safety data.

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 and Drug Safety Center (NPC)

Saudi Food and Drug Authority-Drug sector

3292 Northern Ring Road

Al Nafal District

Riyadh 13312 – 6288

Kingdom of Saudi Arabia

Toll free number: 19999

Fax: 01 2057662

Email: NPC.Drug@sfda.gov.sa

References:

1. Husain, Z., Hussain, K., Nair, R., & Steinman, R. (2010). Diphenhydramine induced QT prolongation and torsade de pointes: an uncommon effect of a common drug. *Cardiology journal*, 17(5), 509-511.
2. Chen, T. Y., Yeh, Y. W., Kuo, S. C., Chen, C. Y., Lin, T. P., & Chang, C. C. (2014). Diphenhydramine dependence through deep intramuscular injection resulting in myonecrosis and prolonged QT interval. *Journal of clinical pharmacy and therapeutics*, 39(3), 325-327.
3. Thakur, A. C., Aslam, A. K., Aslam, A. F., Vasavada, B. C., Sacchi, T. J., & Khan, I. A. (2005). QT interval prolongation in diphenhydramine toxicity. *International journal of cardiology*, 98(2), 341-343.
4. Zareba, W., Moss, A. J., Rosero, S. Z., Hajj-Ali, R., Konecki, J., & Andrews, M. (1997). Electrocardiographic findings in patients with diphenhydramine overdose. *American Journal of Cardiology*, 80(9), 1168-1173.