Azithromycin-induced hiccups

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Hiccups are involuntary and rapid expulsion of air from the lungs with synchronous closure of glottis causing blockade of flow of air. This produces the characteristic hiccup sound. It is modulated by a reflex arc[1] with the afferents as phrenic nerve, vagus and sympathetic chain and the efferents as the phrenic nerve and nerves to intercostal muscles. When hiccups last for more than 48 h, it is termed as persistent hiccups.[1] Drug-induced hiccups are a rare entity and require investigation for other causes or underlying pathologies. We hereby report a rare case of azithromycin-induced hiccups.

Case Report

A 55–year-old male, took self-medication with tablet azithromycin 500 mg once a day, for three days as a treatment for pharyngitis. Within 12 h of intake of first dose of drug, he developed hiccups which were persistent and produced considerable distress. He tried self-medication with tablet metoclopramide and other traditional non-pharmacological measures without relief. Hiccups lasted for three days and stopped at the end of three days when azithromycin was also stopped. There was no history of concomitant drug intake other than metoclopramide. There was no history of diabetes or hypertension. He is a social drinker. However, there was no history of alcohol consumption in the last 24 h of starting of hiccups. There was no clinical evidence of gastrointestinal, central nervous, cardiovascular, renal or metabolic disorder. There was no history of known drug allergies. Laboratory investigations were not carried out. Temporal association of hiccups with the drug was prominent as hiccups started with azithromycin treatment and prompt relief occurred with cessation of drug. Based on Naranjo’s algorithm,[2] the reaction was categorized as possible adverse drug reaction with a score of 4. Based on modified Hartwig and Siegel severity scale, the reaction was categorized as moderate. Rechallenge was not attempted.

Discussion

Hiccup or singultus, a nonspecific symptom, is usually idiopathic. Common causes include gastric distention, stress, sudden change in temperature, alcohol intake and the emotional state. These benign causes are self-limiting. The more serious and uncommon causes require medical or surgical therapy and should not be ignored. These could be due to irritation at any point in the reflex arc or direct central action. Afferent fibers of vagus are irritated in gastric reflux and distention. A foreign body in the ear can irritate the auricular branch of the vagus. Empyema can irritate thoracic vagal afferents. Hepatic disease and pancreatic disease can irritate the diaphragm directly. The CNS pathology can involve the brainstem which has the nuclei for vagus.[3] Drug-induced hiccups are a diagnosis by exclusion of other causes. They are a very unusual side-effect of drugs like corticosteroids, benzodiazepines, general anesthetics, non steroidal anti inflammatory drugs, antidepressants, antipsychotics, methyldopa, digitalis, cisplatin, cyclophosphomide, amoxicillin, cefotetan, ceftiaxone, doxycycline, clarithromycin, imipenem/ cilastatin, ofloxacin, pentamidine, sulfonamides, trimethoprim/ sulfamethoxazole and azithromycin.[1,4] There is only one published report of azithromycin inducing hiccups prior to this case.[4] The mechanism could be modulation of the vagal system by azithromycin.[4] Erythromycin, which has a promotility action, enhances the proximal gastric tone, partially mediated by the vagus.[5] Vagus being a part of the afferent pathway for hiccup, may also be possibly affected by azithromycin. This hypothesis, however, needs to be tested.

Management of drug-induced hiccups starts with withholding the drug and awaiting spontaneous relief. In severe cases, chlorpromazine can be used orally or intravenously. Other drugs used for treatment include metoclopramide, valproic acid, baclofen and nifedipine.[1,3,6] Though this is only the second published report of azithromycin-induced hiccups, there is a chance for gross underreporting, as hiccup is usually neglected as a common occurrence. A more rigorous pharmacovigilance system is needed to get full data on the Indian statistics of drug reactions. This adverse drug reaction has been reported to the Regional Pharmacovigilance Center (South) as per the National Pharmacovigilance Programme of India.

References

1. Mirella G. Drugs may induce hiccups in rare cases. CPJ 2007;140:124-6.

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