

Azithromycin-induced Hiccups

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Abstract

Background: Hiccups are not only known symptoms of some diseases but have been found to be induced by some drugs. In this report, we present a very rare case of azithromycin induced hiccups seen in a young male adult.

Methods: The case records of a 34 year old male who was admitted and successfully managed for sepsis but placed on azithromycin as the only medication at the time of discharge was reviewed.

Results: The patient presented again at the hospital within twelve (12) hours of discharge with a history of severe hiccups which improved significantly with administered chlorpromazine. He was sent home the following day while still on azithromycin. The patient stopped all the medications at home after the second dose of azithromycin due to

persistent drowsiness and decided to take the last dose of azithromycin two days later after realizing that the drowsiness was chlorpromazine induced. He developed another severe episode of hiccups which was successively retreated with oral chlorpromazine.

Conclusion: The patient developed hiccups within 12 hours while he was taking only azithromycin on two (2) different occasions. We then concluded that azithromycin was the probable cause of the hiccups.

Keywords: hiccups, azithromycin, drug-induced adverse drug reaction,

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Introduction

Hiccups (also called hiccoughs or singultus) are involuntary spasmodic contractions of the diaphragm and inspiratory intercostal muscles, halting the start of an inspiration by sudden closure of the glottis^{1,2}. The hiccup reflex arc is a complex interaction between various components of the nervous system: the afferents include the phrenic and vagus nerves as well as the sympathetic chain, a central mediator (not fully determined), and the efferents are made up of the phrenic nerve and accessory nerves connecting to the glottis and inspiratory intercostal muscles^{1,2}. By stimulating any portion of this reflex arc, hiccups may be induced¹. Hiccups usually are transient in occurrence lasting a few minutes to a few days. Drugs are an uncommon cause of hiccups, and in most cases data are lacking to implicate a particular drug³. However, over a 1 year period in France, it was

observed that corticosteroids were the commonest medications associated with hiccups⁴. Others include non-imipramine antidepressants, dopaminergic antiparkinsonians, antibiotics (beta-lactams, macrolides, fluoroquinolones), digitalic compounds, opioids and non-steroidal anti-inflammatory drugs⁴. Drug induced hiccups are a rare entity and require investigation for other causes or underlying pathologies⁵. There are other published reports of azithromycin induced hiccups^{5,6} but none yet in this environment. The most commonly used drug for treatment of hiccups is chlorpromazine 50-100mg daily². Other medications found to be effective include metoclopramide, nifedipine, valproic acid and baclofen².

Case Report

A 34-year-old male was admitted with history of diarrhoea, vomiting and fever – all of two days duration.

No history suggestive of central nervous, respiratory, genitourinary or cardiovascular pathology. Patient did not take alcohol, was not a known diabetic or hypertensive, and not on any regular medication(s) prior to presentation. No past history of persistent hiccups, moderate or severe adverse drug reaction.

On general examination, he was conscious, not pale, anicteric, febrile with a temperature of 38.5°C, 5% dehydrated, not cyanosed, no significantly enlarged peripheral lymph nodes. Abdomen was flat, with mild

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umbilical tenderness ,no rebound tenderness ; abdominal organs were not abnormally enlarged . There were no significant findings on the other systems .

Results of the investigations showed a packed cell volume of 33%, total white cell count of $6.7 \times 10^9 /L$,white cell differentials were neutrophils 65%, lymphocytes 33%, monocytes 1%, basophils 1%, eosinophils 0%. Others include serum sodium 138mmol/L ,chloride 103mmol/L ,potassium 3.8mmol/L ,bicarbonate 24mmol/L ,urea 5.4mmol/L and creatinine 90 μ mol/L. Blood film for malaria parasite was negative. A provisional diagnosis of sepsis was made with focus in the abdomen. He was managed with intravenous saline and glucose infusions, ciprofloxacin and metronidazole and had full recovery after five days on admission but the medications were continued till the 7th day. No history of hiccups before and during admission .At the point of discharge ,he was found to have developed thrombophlebitis at the intravenous access site and was placed on azithromycin 500mg daily for three days as the only medication.

Patient was brought back to the hospital within 12hours of discharge with severe hiccups. No significant findings on examination. There were no clinical features suggestive of gastrointestinal ,central nervous ,cardiovascular ,respiratory ,renal or metabolic pathology .He was commenced on oral metoclopramide 10mg. With no improvement after 2 hours, he was subsequently commenced on oral chlorpromazine 5mg thrice daily and was discharged home the following day while still on azithromycin. The patient stopped all the medications at home after the second dose of azithromycin due to persistent drowsiness. Patient decided to take the last dose of azithromycin two days later after he realized that the drowsiness was due to chlorpromazine .He developed another severe episode of hiccups which was successively retreated with oral chlorpromazine.

Discussion

Diseases involving the gastrointestinal and nervous system can cause hiccups due to the irritation of the phrenic nerve which is one of the efferents of hiccups¹ . Drug medications are generally a rare cause of hiccups. This case of severe hiccups experienced by this patient is a rarely reported drug induced event. The development of hiccups could not be explained by any other mechanism or from use of any of the other medications like metronidazole and ciprofloxacin he had been given because the patient had already recovered from the disease process and medications

stopped before the development of hiccups .The time sequence of development of hiccups within 12 hours of using azithromycin as well as being the only drug the patient was taking at the material time concerned makes azithromycin a strong causal factor. The implication of azithromycin became clearer with the rechallenge done by the patient after skipping the drug for two days.

Based on Naranjo s algorithm the reaction was categorized as probable adverse drug reaction with a score of 5⁷ .Interestingly, the patient involved in this report is a male and drug-induced hiccup has been found to be commoner in males than females^{4,8,9} .There was no history of hiccups within the period of skipping the medications, and this agrees with the reports^{3,4,9} ,which concluded that many cases of drug - induced hiccups will resolve by stopping the drug or decreasing the dose .Resolution time for hiccups have generally ranged from a few hours to a little over a week^{3,4} .

Drug treatment for hiccups most commonly includes chlorpromazine, metoclopramide, nifedipine, valproic acid, and baclofen. Other less frequently used agents are phenytoin, carbamazepine, amitriptyline, methylphenidate, quinidine, haloperidol, perphenazine, and cyclobenzaprine² .Drug induced hiccups may or may not respond to these agents^{3,8, 10} ,as observed in this patient .The azithromycin induced hiccups did not improve with metoclopramide but responded well to chlorpromazine and azithromycin discontinuation.

Conclusion: Without a prior history of hiccups or any other pathologic condition associated with development of hiccups, the patient developed hiccups within 12 hours while he was taking only azithromycin on two (2) different occasions .We then concluded , based also on the time frame that azithromycin was the probable cause of the hiccups .

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