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Rare case report of moxifloxacin-induced persistent hiccups

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SUMMARY

Moxifloxacin is a broad-spectrum antimicrobial agent that is commonly used in clinical practice. Here we report an unusual case of a patient with persistent hiccups caused by moxifloxacin. A man aged in his 40s was treated with moxifloxacin for tuberculous pleurisy. Hiccups occurred 2 hours after intravenous injection of moxifloxacin and lasted into evening. On the second day after injection, hiccups occurred again and made it difficult for him to fall asleep. The clinician ruled out gastrointestinal disease, nervous system disease, electrolyte disturbance and other factors. On assessing causality of the adverse drug reaction, the Naranjo scale for moxifloxacin was six, indicating a probable relationship of hiccups with moxifloxacin. Hiccups stopped 2 min after intramuscular injection of metoclopramide. To our knowledge, this is the first case report about moxifloxacin-induced persistent hiccups. Clinicians should be aware of the rare adverse reaction.

BACKGROUND

Moxifloxacin is a novel fluoroquinolone with potent antibacterial activity against gram-positive, gram-negative and atypical pathogens.¹ Adverse reactions attributed to moxifloxacin include gastrointestinal reaction, hepatic dysfunction, tendinitis and tendon rupture. Hiccups caused by moxifloxacin have never been reported in the literature. This case report brings the attention of clinicians and pharmacists to this rare adverse reaction, so that they can identify and deal with it in time.

CASE PRESENTATION

A man in his 40s was admitted to hospital because he had abdominal pain with fever for two weeks. The patient had a history of AIDS for 10 years, for which he received antiviral drugs including tenofovir, lamivudine, lopinavir and ritonavir tablets. He had no smoking or drinking history, and no drug or food allergies. He had a laparoscopic appendectomy in Taizhou Integrated Traditional Chinese and Western Medicine Hospital 1 week prior to admission. After the operation, the patient received intravenous latamoxef 1 g every 12 hours, but he developed a fever up to 39.9°C with shivers. Laboratory analysis indicated a white blood cell count of $9.7 \times 10^9/L$, a neutrophil ratio of 89.4% and C-reactive protein of 32.74 mg/L. He received intravenous fluconazole 200 mg every 12 hours. Repeated chest computed tomogram (CT) showed left lower lobe infection with left pleural effusion, a few fibrous foci in the lower lobe of the right lung and pericardial effusion. The patient still had fever and chills, but

had no cough, expectoration, nausea, vomiting, dizziness or headaches. He was admitted for further investigation and treatment.

On admission, his vital signs were as follows: temperature 39.6°C, heart rate 100 beats per min, respiratory rate 20 breaths per min and blood pressure 120/67 mm Hg. He had tenderness in the right abdomen, no rebound pain and three laparoscopic opening were seen in his abdomen.

The patient received intravenous piperacillin/tazobactam 4.5 g every 8 hours because of high white blood cell count and C-reactive protein. He was also administered Biktarvy (one tablet daily). Serologic test of HIV RNA was 2.82×10^2 IU/mL and CD4⁺T lymphocyte count was 180/ μ L, T-SPOT.TB > 400 pg/mL. Sputum samples for tuberculosis infection were negative. Chest high-resolution CT showed left pleural cavity (partially encapsulated effusion) with left inferior lobe hypodilation. He received ultrasound-guided drainage of left pleural effusion on day 1, and his pleural fluid sample result was positive for mycobacterium tuberculosis sensitive to rifampicin. For this reason, he was started on tuberculosis treatment. The therapeutic regimen chosen for the patient comprised isoniazide, ethambutol, rifabutin, pyrazinamide and moxifloxacin. After approximately 2 hours of the first intravenous moxifloxacin, this patient began complaining of the onset of hiccups, which were persistent throughout the night. On day 2 of intravenous moxifloxacin, hiccups seriously affected the patient's diet and sleep. Moxifloxacin was suspected to be the most likely cause of hiccups, and was stopped. His hiccups persisted to that night and stopped 2 min after receiving intramuscular injection of metoclopramide.

INVESTIGATIONS

This patient had no previous history of gastro-oesophageal problems or persistent hiccups, no complaints of chest, abdominal or intercostal pain and denied having reflux esophagitis. No positive signs were observed in his nervous system. An MRI of his brain demonstrated no significant findings, and serum electrolyte was also in a normal range. Abdominal CT showed hepatosplenomegaly with a small amount of perihepatic fluid. The attending physician ruled out systemic causes of hiccups. Considering hiccups occurred after intravenous injection of moxifloxacin, clinical pharmacists scored six points according to the Naranjo scale, which combined with patient information, led to the conclusion that the hiccups were probably related to moxifloxacin.



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TREATMENT

This patient received intravenous moxifloxacin 0.4g/day for 2 days and discontinued on day 2 because the persistent hiccups made it difficult for him to fall asleep. His hiccups stopped 2 min after receiving intramuscular injection of metoclopramide. No hiccups were observed at discharge 4 weeks later.

OUTCOME AND FOLLOW-UP

Hiccups were relieved 2 min after receiving intramuscular injection of metoclopramide. There were no hiccups until he was discharged. During follow-up for 4 weeks after discharge, the patient did not report hiccups.

DISCUSSION

Hiccups are caused by a sudden, involuntary powerful spasmodic contraction of the diaphragm and intercostal muscles. It can be divided into three categories based on their duration: acute hiccups last for less than 48 hours, persistent hiccups last for more than 48 hours and intractable hiccups last for more than 1 month.²

There are multiple causes of hiccups in the aetiology, including infections (meningitis, encephalitis), central causes of hiccups (cerebrovascular diseases, demyelinating diseases, brain injury, brain tumours, etc), toxic or metabolic conditions, electrolyte imbalance, thoracic and pulmonary disease, gastrointestinal disease and psychogenic factors (ear, nose and throat diseases, over-excitement, anxiety).^{3,4} In addition, medications can also lead to hiccups, such as azithromycin,⁵ methotrexate,⁶ tramadol,⁷ aripiprazole⁸ and dexamethasone.⁹

This patient demonstrated a sudden and definite case of hiccups shortly after receiving moxifloxacin. Clinicians ruled out gastrointestinal diseases, nervous system diseases or electrolyte disturbance causes of hiccups. The Naranjo scale demonstrated a score of six, indicating a possible relationship between hiccups and moxifloxacin. Hiccups caused by moxifloxacin have not been reported, but levofloxacin-induced hiccups were reported in the literature. Zeng *et al* reported a case of a man treated with levofloxacin injection 0.2g every 12 hours for pneumonia. Hiccups occurred on the third day and did not relieve the next day. Finally, hiccups stopped 30 hours after levofloxacin discontinuation.¹⁰

Moxifloxacin-related hiccups are rare, and the mechanism is not fully understood. The occurrence of hiccup involves a reflex arc including the afferent, central and efferent nerves.¹¹ Hiccups are regulated by central neurotransmitters including 5-hydroxytryptamine (5-HT), gamma-amino-butyric-acid (GABA) and dopamine. Peripheral neurotransmitters regulating hiccups include norepinephrine, epinephrine and histamine.¹² Moxifloxacin is highly lipophilic¹³ and penetrates well through the blood-brain barrier.¹⁴ Moxifloxacin binds to the GABA receptor when it enters central nervous system. GABA is a central inhibitory neurotransmitter involved in hiccup reflex and acts as an inhibitory medium by altering trans-membrane potential.¹² Reducing the binding of GABA or antagonising the GABA receptor can increase phrenic nerve excitability and phrenic spasm, thus leading to hiccup. Another pathway by which moxifloxacin could cause hiccups is that moxifloxacin can stimulate the stomach and cause gastrointestinal dysfunction, which then stimulates the vagus and phrenic nerves.¹⁵

The patient's hiccups relieved after 2 min of receiving intramuscular injection of metoclopramide, which could involve the following mechanisms. First, metoclopramide has important effects on dopamine and serotonergic (5-HT4

agonist) receptors. Metoclopramide can combine with the dopamine receptor, the phrenic nerve could be inhibited and the diaphragm could be relaxed, thus eliminating hiccups.³ Second, metoclopramide can reduce the intensity of oesophageal contractions and relieve the symptoms of hiccups.¹² Third, the effect on serotonergic receptors can promote gastric emptying and reduce both gastric distension and gastro-oesophageal reflux disease (GERD), which is implicated in hiccups.³ As for the rapid relief of hiccups; on the one hand, psychological factors cannot be excluded. On the other hand, the relief time was described by the patient and his family member, and may not be accurate.

In addition to metoclopramide, there are numerous medications are commonly used to treat hiccups. Most of these medications act via dopaminergic or GABA-ergic receptors.³ They are comprised of dopamine receptor antagonist domperidone, GABA-B agonist baclofen and GABA analogue gabapentin. In addition, the antipsychotic chlorpromazine and the anti-epileptic drugs sodium valproate, carbamazepine and gabapentin can also be used for hiccups.³

In conclusion, this is the first case report of hiccups caused by moxifloxacin to our knowledge. The mechanism of hiccups caused by moxifloxacin could be that it enters the cerebrospinal fluid to compete for GABA receptors and stimulate the stomach. Although hiccups are not life-threatening, they can be severely uncomfortable and significantly reduce quality of life, and as such, should not be ignored. Severe hiccups can affect eating, breathing and even sleeping. Therefore, attention should be paid to hiccups caused by moxifloxacin.

Learning points

- ⇒ Persistent hiccups is an unusual case of an adverse effect induced by moxifloxacin; clinicians should be aware of persistent hiccups in patients who receive moxifloxacin.
- ⇒ The mechanism of hiccups caused by moxifloxacin could be that moxifloxacin competes for GABA receptors and stimulates the stomach.
- ⇒ Metoclopramide, haloperidol, benzodiazepines, gabapentin, chlorpromazine and baclofen may be used to treat hiccups caused by moxifloxacin.

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