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Case Report

Moxifloxacin Induced Seizures -A Case Report

Jiana SHI [1, 2], ****Huimin XU*** [1]

1. *Dept. of Pharmacy, the Second Affiliated Hospital, School of Medicine, Zhejiang University, No. 88 Jiefang Road, Hangzhou 310009, China*
2. *Dept. of Pharmacy, Tongde Hospital of Zhejiang Province, Hangzhou 310012, China*

***Corresponding Author:** Email: xuhuiminze@126.com

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Abstract

Background: A 73-year-old female patient developed a generalized tonic-clonic seizure on the 6th day after treatment with moxifloxacin 400 mg daily intravenously for appendicitis. This patient had atrial fibrillation and history of a surgery for intracerebral hemorrhage, with impaired renal function and liver function, but without history of seizures. Moxifloxacin was discontinued and switched to cefuroxime. The patient remained seizure-free at discharge four days later. The naranjo adverse drug reaction probability scale score was 4, indicating a possible adverse reaction to moxifloxacin. The potential risk factors related to moxifloxacin-induced seizures are discussed. It highlights that pre-existing central nervous system disease, elderly female with lower bodyweight and severe renal impairment may be the risk factors involved in moxifloxacin-induced seizures.

Keywords: Fluoroquinolones, Antibiotics, Moxifloxacin, Side effects, Seizures

Introduction

Since the discovery of the first quinolone in 1962, quinolones have become widely used (1). The quinolones are generally considered safe and well tolerated. Central nervous system (CNS) adverse events of quinolones occur at an overall incidence of 1%–2% (2). Moxifloxacin is a fourth-generation fluoroquinolone with potent activity against gram-positive, gram-negative, atypical, and anaerobic bacteria (3). Moxifloxacin shows less potential for causing CNS-related adverse events compared with other fluoroquinolones (norfloxacin, sparfloxacin, ciprofloxacin, and ofloxacin) (4).

There is only one case of moxifloxacin-induced seizures published in English in databases such as Google Scholar, MEDLINE, Cochrane and Ovid (5). Here, we report a case of an elderly woman who developed seizures after treatment with moxifloxacin and had no history of seizures. Potential risk factors taking place in this patient as well as in previous published case of moxifloxacin-induced seizures are discussed.

Case report

A 73-year-old, 45-kg Asian woman was hospitalized with chest distress, shortness of breath, abdominal pain, and unable lying down. Her medical history included atrial fibrillation and a surgery for intracerebral hemorrhage. She had left sided paralysis, but no previous history of seizures. She did not consume alcohol and no other major organ diseases. She had a history of "penicillin allergy" documented as vomiting. No allergies to other drugs, foods and pollens were reported. She had been taken Chinese herbs for constipation 1 week prior to admission.

In the emergency center, her vital signs were: blood pressure 109/65 mm Hg, heart rate 71 beats per min, respiratory rate 20 breaths per min, and tympanic temperature 36.3 °C. She appeared abdominal tenderness, trace edema to the lower limbs. Crackles were audible diffusely throughout the lungs with no wheezing. The muscle strength of left upper limb was level 0 and the left lower limb was level 2. The bilateral Babinski's sign was positive. The rest of the physical examination was within normal limits. Laboratory tests included N-terminal pro B-type natriuretic peptide of > 35000 pg/mL (normal range, 0-100 pg/mL), total bilirubin of 26.7 μmol/L (normal range, 3.4-20.5 μmol/L), alanine aminotransferase of 413 U/L (normal range, 0-34 U/L), aspartate aminotransferase of 385 U/L (normal range, 0-34 U/L),, serum urea nitrogen of 17.92 mmol/L (normal range, 2.8-7.2 mmol/L), serum creatinine of 151 μmol/L (normal range, 53-133 μmol/L) and C-reactive protein (CRP) of 31.5 mg/L (normal range, 0-10 mg/L). Creatinine clearance calculated using Cockcroft-Gault equation was 20.8 mL/min. A complete blood cell count revealed a decreased platelet count of 45×10^9/L (normal range, 100-300 $\times 10^9$/L), and an increased white blood cells (WBC) count of 15.3×10^9/L (normal range, 4-10 $\times 10^9$/L), with high neutrophils percentage of 90.0% (normal range, 50%-70%). Her abdominal ultrasound findings suggested appendicitis.

The patient received intravenous administration of moxifloxacin 400 mg once daily for appendicitis after she was admitted to the cardiovascular ward. Other medications administered intravenously were furosemide (20 mg daily), dopamine (80mg daily), pantoprazole (40 mg daily), magnesium isoglycyrrhizinate (150 mg daily), and polyene phosphatidylcholine (465 mg daily). Accompanied medications administered orally were isosorbide mononitrate (40 mg daily) and aspirin (100 mg daily). She was clinically improving at that time, with a decrease in WBC count and CRP. On the morning of day 6, two hours before the 6th administration of moxifloxacin, the patient experienced a tonic-clonic seizure lasting 5 minutes. At the time of the seizure, there were no abnormal findings on electrocardiogram, blood pressure and oxygen saturation. Her serum calcium concentration was 1.79 mmol/L (normal range, 2.05-2.60 mmol/L) and sodium concentration was 128.1 mmol/L (normal range, 135-145 mmol/L), which were slightly lower than normal limits. Her serum potassium concentration, blood glucose, and thyroid hormone levels were unremarkable. She refused to take computed tomography scan of her brain. Moxifloxacin was discontinued and switched to cefuroxime. The patient remained seizure-free at discharge four days later.

Discussion

Seizures can arise from any disorder, event or disease that damages the brain and simulates unusual electrical activity. In our patient, seizures appeared after treatment with moxifloxacin and did not reoccur when moxifloxacin was discontinued. The Naranjo adverse drug reaction probability scalescore (6) was 4, indicating a possible relationship between seizures and moxifloxacin use.

Quinolone-related seizures are rare and serious adverse events. The exact mechanism by which quinolones induce seizures is not to date fully understood. There appears to be an association between the chemical structures of the quinolones and the risk of seizures (7,8). Lipophilicity of a compound may affect the extent of its penetration into the CNS, and thus affects the risk of CNS adverse effects. Moreover, the displacement of g-aminobutyric acid (GABA) from its receptors by quinolones is considered as another mechanism for CNS excitation. Quinolones containing 7-piperazine (e.g., ciprofloxacin, enoxacin, and norfloxacin) and those containing 7-pyrrolidine (e.g., tosufloxacin and clinafloxacin) appear to displace GABA or compete with GABA binding at the receptor sites within the CNS, resulting in stimulation (7). Quinolones with increased CNS penetration, coupled with unsubstituted piperazine or pyrrolidine groups at the 7 position, are considered to be associated with a higher risk for seizures (9). Moxifloxacin is highly hydrophilic and lipophilic (10), penetrates well through the blood-brain barrier (11), but lacks the specific structure-

toxicity relationships noted to induce seizures (12). Moxifloxacin shows low excitatory potency in vitro models of evoked potential in rat hippocampus slices (13) and no significant CNS adverse effects in clinical studies (14) compared with other fluoroquinolones.

In addition to the chemical properties of the quinolones, quinolone-related seizures are most likely to occur in a susceptible population with predisposing factors, such as renal or hepatic insufficiency, electrolyte imbalances, the elderly, pre-existing CNS disease (epilepsy, cerebral trauma, intracranial mass, anoxia etc), or concomitant use of proconvulsant drugs (14-16). Our patient had both impaired renal function and liver function with increased age. She had no history of seizures but had a history of cerebral surgery for intracerebral hemorrhage. Her serum calcium and sodium levels were slightly lower than normal limits at the time of the seizure. She had not coadministration with nonsteroidal anti-inflammatory drugs (such as fenbufen or its metabolite biphenylacetic acid) or theophylline, which has been reported to potentiate the likelihood of seizures with some quinolones (2). Our patient shared some common characteristics with the first case published in the literature of moxifloxacin-related seizures reported by Qiao and colleagues (5). They were both Asian women, had severe impaired renal function and histories of pre-existing CNS diseases (that patient had a history of spina bifida) but no histories of seizures or epilepsy. Unlike our patient, that patient was only 23-year-old. Pre-existing CNS disease might predispose to moxifloxacin-related seizures by lowering seizure threshold. Advancing age may be not a necessary predisposing factor for moxifloxacin-induced seizures because pharmacokinetics values of moxifloxacin are unaffected by age and no dose adjustment is necessary in elderly patients (17). However, elderly females may be a risk for moxifloxacin-induced seizure because a study of pharmacokinetics of moxifloxacin showed that maximum plasma concentration (Cmax) and area under the plasma concentration-time curve (AUC) were higher and clearance was lower in elderly females than elderly males due to elderly females' lower bodyweights (17). Moreover, although the potential for moxifloxacin accumulation is low in patients with renal or hepatic impairment because moxifloxacin is eliminated by multiple clearance pathways, renal dysfunction does result in changes in the plasma pharmacokinetics of metabolite acylglucuronide (M2) of moxifloxacin, causing greater and longer exposure (18). This report suggests physicians to pay attention to the potential risk of moxifloxacin-induced seizures, especially in elderly female patients with lower bodyweight and pre-existing CNS disease and severe renal impairment, when using the regular dosage of moxifloxacin and should monitor the patients closely.

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