CASE REPORT

Levofloxacin-Induced Oromandibular Dystonia in a 9-Year-Old Patient

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ABSTRACT

Extrapyramidal symptoms (EPS) that include akathisia, dystonia, pseudoparkinsonism, and dyskinesia are abnormal movements commonly induced by antipsychotic medications. These symptoms are also associated with specific non-antipsychotic agents. This case report describes a case of a 9-year-old boy on antibiotics treatment that developed EPS.

A 9-year-old boy presented to the emergency department of Imam Hossein Children›s Hospital with chief complaints of trismus, difficulty speaking, and tongue protrusion. One week before these presentations, he had been prescribed Tavanex® (levofloxacin) and clindamycin. His symptoms improved after the withdrawal of antibiotics and administering Biperiden, and he was discharged in good condition. On a follow-up visit one week after discharge, no remaining symptoms were present, and he was in good condition.

Based on the questions in the Naranjo criteria, levofloxacin receives a score of 7 and is a probable cause of adverse drug reaction (ADR). Clindamycin, with a score of 6, is also a probable cause for this adverse drug reaction, but clinical judgment was in favor of levofloxacin as the culprit.

Clinicians should be aware of the potential EPS of levofloxacin at standard doses. Effective management of adverse events is necessary to ensure patient safety and optimal outcomes.

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Introduction

Extrapyramidal symptoms (EPS), including akathisia, dystonia, pseudoparkinsonism, and dyskinesia, are abnormal movements commonly induced by antipsychotic medications (1). EPSs are caused by dopamine blockade or depletion in the basal ganglia, which mimics idiopathic pathologies of the extrapyramidal system (2). These symptoms range from minimal discomfort to permanent muscular movements, and they can occur after one dose of the antipsychotic medication or several weeks after the beginning of therapy. Today, EPSs are not seen as frequently because of the use of newer therapeutic antipsychotic agents and prophylactic therapy (3). Currently, available treatments for these disorders are primarily symptomatic and are often linked with several detrimental side effects (4).

These symptoms are also associated with certain non-antipsychotic agents, including some antidepressants, lithium, various anticonvulsants, antiemetics, and, rarely, oral contraceptive agents (2). Some cold medications (decongestants), anticonvulsants, antihistamines, and selective serotonin reuptake inhibitor antidepressants may increase the risk of EPSs (5, 6). EPSs caused by these agents are indistinguishable from neuroleptic-induced EPSs (2).

The active ingredient levofloxacin belongs to the group of drugs called fluoroquinolones, an antibacterial (antibiotics) with bactericidal activity. Fluoroquinolones have been a popular class of antibiotics for various infections. The newer fluoroquinolones have retained much of the activity of ciprofloxacin and ofloxacin against enteric gram-negative bacteria. Ofloxacin is a racemic mixture of two stereoisomers, whereas levofloxacin is composed solely of the active stereoisomer (7). Thus, levofloxacin has the same spectrum of activity as ofloxacin but is generally twofold more potent.

Newer drugs in this class have been developed with a broader spectrum of activity, including better coverage of gram-positive organisms and, in one case, even anaerobes. However, toxicities have been associated with some of these newer agents. Fluoroquinolones are the only class of antimicrobial agents in clinical use that are direct inhibitors of bacterial DNA synthesis. Common adverse effects associated with fluoroquinolones include gastrointestinal and central nervous system toxicities. Other adverse effects include rashes and other allergic reactions, tendinitis and tendon rupture, QT prolongation, hypoglycemia and hyperglycemia, and hematologic toxicity. The fluoroquinolone drugs are generally well tolerated. Some medications of the levofloxacin family can cause EPS and muscle conduction disorders. Although EPSs are reported with the use of quinolone antibiotics in some other previous case reports (8-11), these adverse effects are rare with these drugs. Extrapyramidal disorders and other neurologic disorders are reported with the use of quinolones in clinical studies and on extensive post marketing experience (8-22).

This article describes a 9-year-old boy on levofloxacin treatment who developed EPS in a rare clinical setting. Reporting this case is vital because informing clinicians about possible levofloxacin-induced EPS can prevent future undesirable consequences of similar events.

Case Presentation

A 9-year-old boy presented to the emergency department of Imam Hossein Children's Hospital with chief complaints of lower jaw spasm, drooling, dysphagia, dysarthria, irritability, tongue protrusion, and torticollis one day before admission. He was a known case of common

variable immunodeficiency (CVID) with a history of receiving intravenous immunoglobulin (IVIg), seizure disorder (no medication), and asthma (no medication). He had a history of allergies to tomatoes, eggplant, peanuts, and walnuts. His growth and development were normal. One week before this presentation, he had been prescribed Tavanex® (levofloxacin) 500 mg tablet (250 mg q 12 hours) and clindamycin 150 mg capsule (150 mg q 8 hours) for his diagnosed septic arthritis in left knee (first he had received ceftriaxone in the hospital and discharged with cefixime but due to a fever three days after discharge, clindamycin and levofloxacin were prescribed by an infectious disease specialist). He was also receiving a 20 mg capsule of pantoprazole each morning. He had a history of Imipramine use for his urinary incontinence, but the drug was discontinued some months ago. So, his medications at the presentation were clindamycin, levofloxacin, and pantoprazole. The patient had intermittent symptoms without lateralization. In the first clinical examination, tongue protrusion was intermittent and lasted one minute. He had to insert his tongue back into his mouth with hand aid. He had sialorrhea, muffled and unrecognizable speaking, and an inability to open his mouth. Neurologic examinations otherwise were normal. Biochemical and hematologic evaluation was normal.

Considering the likelihood of incidence of EPS with the use of antibiotics, the infectious consult recommended discontinuing antibiotics. Antibiotics were discontinued, and for his dystonia, 3 mg of intramuscular biperiden was administered immediately. Oral biperiden at a dose of 2 mg every 12 hours was prescribed for the next 24 hours. His dystonia and tongue protrusion improved by antibiotics withdrawal and biperiden administration. After one day, he was discharged in good condition. At the follow-up visit one week later, no signs and symptoms were present.

Discussion

Neurotoxic manifestations associated with quinolone include seizures, confusion/encephalopathy, myoclonus, and toxic psychosis (23). New quinolone derivatives or gyrase inhibitors include levofloxacin, sparfloxacin, grepafloxacin, trovafloxacin, gatifloxacin, and moxifloxacin and are the most commonly implicated drugs causing neurotoxic side effects among quinolones. These were first described with the use of ofloxacin (24). Levofloxacin is reported to cause pronounced acute delirium associated with psychotic features (25) as well as seizures (21). In postmarketing reports, CNS toxic effects of gyrase inhibitors have an incidence of 0.89%, with primary symptoms listed as headache, insomnia, dizziness, restlessness, and, less commonly, delusions and hallucinations (22). Oro-facial dyskinesias have also been reported with quinolones. The drugs implicated include ciprofloxacin and ofloxacin in the absence of a metabolic abnormality and at extremes of age (18, 19). In one case, a 71-year-old male presented with spitting, profuse sweating, insomnia, echolalia, echopraxia, orofacial and limb automatisms, and hypersalivation. This Tourette-like syndrome begs a possible interaction of ofloxacin with the central dopaminergic system (12). Quinolone treatment also resulted in extrapyramidal manifestations (8).

In one extensive analysis of 6775 patients, CNS manifestations occurred in approximately 2.8% of patients given gemifloxacin, with 1.2% complaining of headache and 0.8% dizziness

(17). As postulated for fluoroquinolone-induced seizures, disruption of the GABAergic system is implicated in the development of fluoroquinolone-induced orofacial dyskinesias (9). Variability in the binding potency of quinolones to the GABA-A receptors may explain the variability in neurotoxic effects (26).

Postulated mechanisms for fluoroquinolone-mediated CNS toxicity include inhibition of GABA-A receptors and activation of excitatory NMDA receptors (14).

The close temporal relationship between levofloxacin administration and EPS suggests a causal association. To further support levofloxacin-related EPS, Naranjo criteria were used to evaluate the likelihood of the adverse drug reaction. The Naranjo criteria include ten questions to rate adverse drug reactions using a numeric score that ranges from -4 to +13 (Table 1). Based on the questions in the Naranjo criteria, levofloxacin receives a score of 7 and has a probable adverse drug reaction (ADR). Clindamycin receives a score of 6 based on this criteria. So, clindamycin is also a probable cause for this adverse drug reaction.

Although uncommon, some other case reports have demonstrated extrapyramidal and other nourologic symptoms from flouroquinolone therapy. An 83-year-old man was admitted for right lower lobe pneumonia, which did not improve after a five-day outpatient treatment with amoxicillin/clavulinate and clarithromycin. An empiric treatment with levofloxacin was initiated, with a significant improvement after 24 hours of

Table 1. Naranjo scale

Question	Yes	No	Do not know	Score of levofloxacin	Score of clindamycin	Score of pantoprazole
Have there been previous conclusive reports on this reaction?	+1	0	0	1	0	0
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2	+2	+1
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	+1	0	0	+1	+1	+1
Did the adverse reaction reappear when the drug was readministered?	+2	-1	0	0	0	0
Are there alternative causes (other than drugs) that could, on their own, have caused the reaction?	-1	+2	0	+2	+2	-1
Did the reaction reappear when a placebo was given?	-1	+1	0	0	0	0
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0	0	0
Was the reaction more severe when the dose was increased? or less severe when the dose was decreased?	+1	0	0	0	0	0
Did the patient react similarly to the same or similar drugs in previous exposures?	+1	0	0	0	0	0
Did any objective confirm the adverse event?	+1	0	0	+1	+1	0
Total score				+7	+6	+1

this treatment. On the third day of hospitalization, the patient developed delirium while he was afebrile and with normal blood oxygenation. Treatment with levofloxacin was stopped, and a complete resolution of the patient's delirium was observed two days later. The authors reported that this was the third case of levofloxacin-induced delirium described in the medical literature (15).

Another healthy 42-year-old woman presented with acute-onset delirium with psychotic features as a consequence of levofloxacin therapy. Withdrawal of the medication was associated with the return of the patient's normal mental status (27).

Another study reported a 43-year-old man who developed orofacial dyskinesia three days after starting ofloxacin treatment. Three days after initiating ofloxacin, he developed extrapyramidal choreoathetotic movements of the face. Involuntary facial grimacing movements and an inability to close the jaws occurred continuously in this fully conscious patient (19).

In another report, a five-year-old male child was admitted with a history of fever for eight days. The child was started on oral ciprofloxacin (15 mg/ kg/day) in two divided doses and oral paracetamol (15 mg/kg) when required. On the third day, the child developed uprolling of the eyes with torticollis and increased tone of all four limbs with abnormal posturing. The patient was given parenteral (IV) diazepam (0.4 mg/ kg) immediately, following which he had an uneventful recovery from this episode (13).

Clindamycin is not known to have major neurotoxic effects (23). Although no reports were found on EPS with the use of clindamycin, in the present case, it is not unlikely and should be considered a possible cause of this reaction because of co-administration with levofloxacin. However, clinical judgment is in opposition to clindamycin's adverse effects.

In Conclusion

Clinicians should be aware of the potential adverse reactions of levofloxacin at standard doses. Effective management of adverse events is necessary to ensure patient safety and optimal outcomes.

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None.

Authors' Contribution

Mohammad-Reza Ghazavi was the physician of this patient. All of the interventions and treatments and reviewing the manuscript were under supervision of him. Dr Zahra Allameh suggested to report this case and wrote the manuscript.

Conflict of Interest

None.

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