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【 CASE REPORT 】

Levofloxacin-associated Encephalopathy with Severe Hyperventilation

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Abstract:
A 64-year-old woman with no previous mental illness took a single 500 mg tablet of levofloxacin for cystitis. Two hours later, she developed psychosis with involuntary movement and severe hyperventilation with respiratory alkalosis. Cranial magnetic resonance imaging findings were unremarkable, and an electroencephalogram revealed no epileptiform discharge. Her symptoms improved on the third day after levofloxacin was discontinued. Levofloxacin-associated encephalopathy with psychotic features is a rare adverse event. Disturbance of gamma-aminobutyric acid-ergic (GABAergic) interneurons by levofloxacin may lead to hyperventilation via dysfunction of the brainstem respiratory network. Physicians should be aware of hyperventilation as an additional serious symptom of levofloxacin-associated encephalopathy in acute settings.

Key words: levofloxacin, psychosis, antibiotic-associated encephalopathy, central nervous system toxicity, hyperventilation

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Introduction

Levofloxacin, which is the active isomer of ofloxacin, is a third-generation fluoroquinolone antibiotic that has a broad antibacterial spectrum and is widely used. Pooled safety data for levofloxacin (n=7,537) suggest that the most common adverse drug reactions leading to discontinuation of the medication are gastrointestinal adverse reactions (1.4%), nausea (0.6%), vomiting (0.4%), dizziness (0.3%), and headache (0.2%) (1). The safety and efficacy of levofloxacin have been well documented, and central nervous system (CNS) toxicity is low, occurring in just 1 out of every 6 million prescriptions (2, 3).

We herein report a case of acute psychotic symptoms with severe hyperventilation after a patient took one tablet of levofloxacin. This is the first report describing hyperventilation as an adverse effect of quinolones.

Case Report

A 64-year-old woman had increased urinary frequency and experienced an uncomfortable feeling while urinating for several days. A urologist diagnosed her with cystitis and prescribed levofloxacin. Two hours after taking a single 500 mg tablet of levofloxacin without any other medicine, the patient became restless and confused. She visited the clinic again and was referred to our hospital for a further examination and treatment.

The patient had undergone mastectomy for right breast cancer and received chemotherapy seven years earlier. She had been subsequently followed up with no signs of recurrence. She had no history of a confusional state and no documented disorders of the central nervous system. She was a non-smoker and did not have any history of alcohol misuse or antipsychotic drug use.

On a physical examination, the patient's temperature was 37.8 °C, and she had a blood pressure of 115/56 mmHg, a heart rate of 114 beats per min, and a respiratory rate of 34 breaths per min. She was confused and disoriented and was becoming agitated. We observed bilateral mild muscular rigidity in the upper and lower limbs and involuntary movement characterized by dyskinesia. She had no episodes of autonomic instability such as hyperhidrosis or convulsions. The patient reported visual hallucinations, saying "a baby boy is lying next to me" and repeating many times that "he

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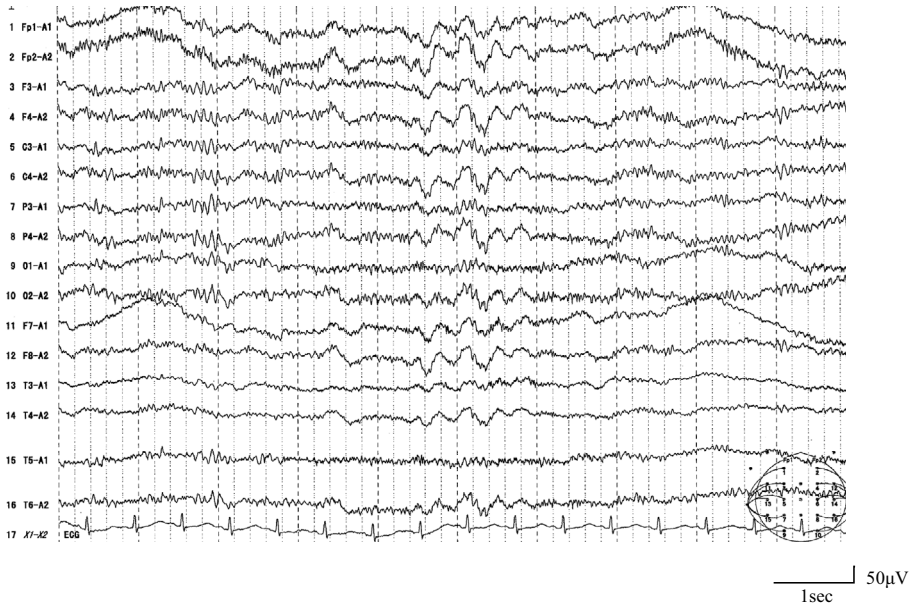

Figure. An electroencephalogram on the second day showed intermittent rhythmic delta activity with background beta activity but no epileptiform discharge.

is going to die".

Laboratory examinations determined a white blood cell count of 8,300/μL, hematocrit of 32.6%, platelet count of 30.7×10^4/μL, serum creatinine level of 0.85 mg/dL, blood urea nitrogen (BUN) level of 16.4 mg/dL, sodium level of 140 mEq/L, potassium level of 2.7 mEq/L, aspartate transaminase level of 53 U/L, alanine aminotransferase level of 42 U/L, lactate dehydrogenase level of 275 U/L, C-reactive protein level of 20.1 mg/dL, thyroid stimulating hormone level of 2.66 μIU/mL, and NH_3 level of 20 μg/dL. An assessment of the patient's blood gas revealed a pH of 7.82, carbon dioxide partial pressure (pCO_2) of 10.3 mmHg, partial pressure of oxygen (pO_2) of 165 mmHg, and HCO_3 of 17.6 mmol/L. Anti N-methyl-D-aspartate (NMDA) receptor antibody was not detected. Chest X-ray showed no active lesions, and head computed tomography (CT) and brain magnetic resonance imaging (MRI) showed no abnormal findings. Whole-body CT and MRI to assess the abdomen and pelvis revealed no active or tumorous lesions. A cerebrospinal fluid (CSF) analysis provided a white cell count of 1 cell/μL, with glucose and protein levels of 66 mmol/L and 14.2 g/L, respectively. An electroencephalogram (EEG) on the second day showed intermittent rhythmic delta activity with background beta activity but no epileptiform discharge (Figure).

The patient presented with hyperventilation with a respiratory rate of approximately 90 breaths per min and exacerbation of severe respiratory alkalosis. Her hyperventilation improved gradually on the third day of admission following the injection of 10 mg haloperidol in addition to 10 mg diazepam.

At admission, after the patient discontinued levofloxacin, meningoencephalitis was suspected, so she was treated with antibiotic medication (vancomycin, ceftriaxone, ampicillin, and acyclovir). On the fourth day, she was able to say her name but remained drowsy and showed coarse tremor in all her limbs. Since these symptoms were improving, medication was stopped on the fourth day of admission. On the fifth day, the patient became mostly alert and oriented but still had impaired attention, with a Mini-Mental State Examination score of 25. She was discharged after 17 days without any neurological deficits.

Discussion

Although medications are commonly considered a reversible cause of encephalopathy, antibiotics are underrecognized in the etiology of the condition. In this case, the temporal relationship between the patient's consumption of levofloxacin and the acute alteration in her level of consciousness suggested that levofloxacin was the precipitant of the psychotic symptoms. Bhattacharyya et al. (4) conducted a review and proposed the concept of antibiotic-associated encephalopathy (AAE). They classified AAE into three types, with quinolones belonging to Type 2 AAE, which is characterized more by predominant psychotic symptoms than seizures or myoclonus. AAE arises within days of antibiotic administration and resolves after antibiotic discontinuation. Due to the marked improvement observed on discontinuing levofloxacin in this case, we diagnosed the condition as levofloxacin-associated encephalopathy, and the original cause of the fever was presumably cystitis.

To our knowledge, there have been 12 case reports, including the present one, on levofloxacin-associated encephalopathy (5-15) (Table). The patients ranged in age from 13-83 years (mean, 46 years old). The dose of levofloxacin administered ranged from 300 to 500 mg/day, and all patients showed symptoms of psychosis, while 2 presented with ex-

Table. Previously Reported Cases of Levofloxacin-associated Encephalopathy.

Case no.	RN	Age	Sex	Underlying disease	Reason for prescription	Renal failure	Daily dose	Time to symptom onset	Recovery time after discontinuation	EEG	MRI/CT	CSF	Other symptoms	Prognosis
1	5	67	M	Gall bladder cancer and alcohol dependence	Flu	N	300 g/day p.o.	4 days	1 day	ND	ND	ND	Involuntary movements and convulsions	Good
2	6	73	M	NP	Pneumonia	N	500 mg/day p.o.	2 days	2 days	ND	No specific finding	ND	NP	Good
3	7	50	M	Diabetes mellitus and hypertension	Pneumonia, UTI and cellulitis	N	500 mg/day p.o.	3 days	2 days	ND	ND	WNL	NP	Good
4	8	42	F	NP	Sinusitis and UTI	N	500 mg/day p.o.	2 days	2 days	ND	ND	WNL	NP	Good
5	9	83	M	Coronary bypass surgery and breast carcinoma	Pneumonia	Y	500 mg/day IV	3 days	2 days	Slow background activity	ND	WNL	Extrapyramidal syndrome	Good
6	10	55	M	Hypertension and inguinal hernia	Pneumonia	Y	500 mg/day IV	6 days	2 days	WNL	WNL	ND	NP	Good
7	11	13	F	NP	Acute bronchitis	N	500 mg/day p.o.	2 h	4 days	WNL	WNL	WNL	NP	Good
8	12	38	M	Multiple sclerosis and hepatitis C	Pneumonia	N	500 mg/day p.o.	3 days	1 day	ND	ND	ND	NP	Good
9	13	28	M	NP	Pneumonia and UTI	N	500 mg/day p.o.	3 days	2 days	ND	ND	WNL	NP	Good
10	14	17	M	Synovial sarcoma with metastasis	Pneumonia	ND	500 mg/day IV	35 min	4 h	ND	ND	ND	NP	Good
11	15	22	F	NP	UTI	N	500 mg/day p.o.	3 h	3 days	ND	ND	ND	NP	Good
12	(Present case)	64	F	Breast cancer	Cystitis	N	500 mg/day p.o.	2 h	4 days	Intermittent rhythmic delta activity with background beta activity	WNL	WNL	Hyperventilation, involuntary movement, and rigidity	Good

R.N: reference number, M: male, F: female, NP: none present, UTI: urinary tract infection, IV: intravenous, N: no, Y: yes, ND: not described, p.o.: per os, EEG: electroencephalogram, MRI: magnetic resonance imaging, CT: computed tomographic scanning, WNL: within normal limits, CSF: cerebrospinal fluid

tra pyramidal signs. An EEG was performed in just four patients, with only one patient other than our own showing slow background activity and none showing epileptiform discharge. Head CT and brain MRI as well as CSF examinations revealed no specific findings. Psychotic symptoms occurred between 2 hours and 3 days after the oral intake of levofloxacin. In most cases, prompt discontinuation of levofloxacin let to improvement within 48 hours of onset.

Similar to the findings in 1 previously reported case (11), psychotic symptoms appeared 2 hours after taking a 500 mg tablet of levofloxacin in our case and improved within 36 hours after discontinuation of the drug. Levofloxacin is rap-

idly absorbed from the gastrointestinal tract, with the time to maximum plasma concentrations (T max) ranging from 0.8 to 2.4 hours after the administration of 50-1,000 mg with or without food (16). Therefore, while the time to the onset of symptoms was shorter in this case than in previously reported cases, that psychosis developed just 2 hours after the oral intake is not unexpected. According to previous reports, the mean age of patients with an acute onset (not including our patient) was 17.3 years, whereas the mean age of the patients with a relatively late onset was 54.5 years. Although the acute development is more frequent in young patients than in older ones, this might be due to the blood-brain barrier influencing the concentrations of levofloxacin in the brain tissue to a variable degree (17). Additional case reports will be required to confirm the etiology associated with a more acute onset.

Previous studies have suggested that the pathophysiology of levofloxacin-associated encephalopathy is associated with a disturbance of gamma-aminobutyric acid-ergic (GABAergic) interneurons. Quinolones affect the central nervous system mainly by inhibiting GABA receptor binding, which is concentration-dependent (18). Some animal models suggest that the onset of psychosis involves dysfunction of GABAergic interneurons, leading to excessive cortical glutamatergic activity, which in turn mediates subcortical dopamine activity (19).

In the present case, in addition to psychotic features, the patient experienced prominent ventilation disturbance. This is the first report describing hyperventilation as an adverse effect of quinolones. Hyperventilation persisted for approximately 36 hours with respiratory alkalosis, with the pH increasing to 7.82 on blood gas examinations. The major cause of central neurogenic hyperventilation is infiltrative tumors involving the brainstem (20). However, there are a few cases of hyperventilation caused by anti-NMDA receptor encephalitis (21, 22). An antibody-mediated decrease in NMDA receptors predominantly inactivates GABAergic neurons and leads to many clinical features of the disorder (23).

The generation of ventilatory rhythm via the brainstem derives from a complex interplay between several brainstem sites. The NMDA receptor system may play an excitatory role in several steps leading both to the augmentation and termination of inspiration (24). As in cases of anti-NMDA receptor encephalitis, impaired GABAergic interneurons may lead to hyperventilation via dysfunction of the brainstem respiratory network. In addition, other symptoms, including extrapyramidal signs, such as rigidity and dyskinesia, can also be caused by the disinhibition of dopaminergic and glutaminergic neurons arising from the same neuronal network disturbance as in anti-NMDA receptor encephalitis. Both hyper- and hypoventilation can also be explained based on a functional neurotransmitter imbalance which is predominantly characterized by the presence of hypo-GABAergic tone and glutamatergic hyperactivity (23). Therefore, it may be important to identify altered respiratory rhythm patterns in cases of levofloxacin-associated encephalopathy.

Conclusion

Levofloxacin-associated encephalopathy characterized by psychotic features is a rare adverse event that can occur within two hours after taking a single tablet. In addition, the disturbance of GABAergic interneurons by levofloxacin may lead to hyperventilation via dysfunction of the brainstem respiratory network. Physicians should be aware of hyperventilation as an additional serious symptom of AAE in acute settings.

Author's disclosure of potential Conflicts of Interest (COI).
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