

Suspected Quinolone-induced Cognitive Impairment: A Case Report

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Abstract

Cognitive impairment is a change in baseline functioning of cognitive processes that may include perception, memory, learning, thinking, verbal abilities, problem solving, and/or motor performance. One specific neuropsychiatric condition is delirium, an acute onset syndrome with a fluctuating course. Risk factors include prior cognitive impairment, advanced age, infection(s), and medication. Ciprofloxacin and levofloxacin are quinolones, one class of medications associated with cognitive changes. Adverse drug effects include confusion and delirium. We report a case of cognitive impairment secondary to levofloxacin use.

Introduction

Several drug classes, including antibiotics, have been associated with changes in cognitive functioning, such as alterations in perception, impaired memory, learning, reasoning, and verbal abilities, in susceptible individuals. However, only a few case reports have been published related to the extent to which quinolones, a class of antibiotics, may be associated with cognitive impairment.

A review of the psychiatric and neurologic literature revealed eight cases of acute psychosis¹⁻⁸ and eight cases of delirium⁹⁻¹⁶ associated with ciprofloxacin, pefloxacin, and levofloxacin. Although rare, quinolone antibiotics have been associated with cognitive impairment, often in a concentration dependent manner. Drug clearance through the liver and kidneys decreases with age, thereby increasing the risk of drug-induced cognitive changes. Most quinolones are primarily cleared by the kidneys. This places adults 65 years and older at a higher risk of quinolone-induced cognitive impairment, particularly delirium and drug-induced psychosis due to declining renal function. Delirium is a syndrome with an acute onset and fluctuating course characterized by reduced clarity of awareness of the environment and a change in cognition or the development of perceptual disturbance due to a medical condition or medication.¹⁷ Drug-induced psychosis is characterized by the rapid onset of impaired thought and emotions and loss of contact with external reality.¹⁸

Case Report

A 67-year-old woman with a history of schizoaffective disorder, bipolar type, panic disorder and history of renal transplantation participates in an intensive case management community-based program. The patient is seen three times weekly by the case managers or one of the psychiatric nurses and once monthly in clinic by the team psychiatrist and psychiatric resident physician. When she was seen in her home for a regularly scheduled visit, she was observed to have difficulty with number sequences and specific tasks. The onset was sudden, and this presentation persisted when she was seen by her primary care physician (PCP) several days later. At that time her PCP ordered lab work, including a urinalysis, and a work-up for a transient ischemic attack (TIA).

Metabolic panel and complete blood count were normal. Her BUN was 17 mg/dL (range 7-25), Cr 0.88 mg/dL (0.50-0.99), eGFR (non-African-American) 68 mL/min/1.73m² and estimated creatinine clearance was 61 mL/min, modified for patient's weight. The TIA work-up was negative. The urinalysis, however, revealed a urinary tract infection. A 14-day course levofloxacin 250 mg daily was prescribed, completed, and added to an already complex medication regimen including divalproex sodium 1000 mg at bedtime, olanzapine 2.5 mg at bedtime, trazodone HCl 25 mg at bedtime, mycophenolate mofetil 500 mg twice daily, tacrolimus 1.5 mg twice daily, omeprazole 20 mg each morning, furosemide 40 mg each morning, metoprolol tartrate 50 mg daily, glimepiride 4 mg each morning, atorvastatin calcium 20 mg each morning, cinacalcet HCl 30 mg daily, mirabegron 25 mg daily, and prednisone 5 mg daily.

The original patient presentation of cognitive impairment persisted until 24 hours following cessation of levofloxacin, after which she returned to baseline. When seen in psychiatric clinic one week later, she was correctly oriented; immediate, recent, and remote memory were intact.

Discussion

As has been previously identified, the primary causes of delirium are underlying medical conditions, medications, or drug withdrawal.¹⁹ In the above case, there are several possible etiologies of the patient's sudden mental status change including the urinary tract infection and the complex pharmacologic regimen. However, the abrupt resolution of the symptoms coincided with the cessation of levofloxacin, suggesting that levofloxacin therapy contributed at least partially to this patient's presentation.

Although rare, quinolone antibiotics can cause cognitive impairment, often in a concentration-dependent manner. This places the elderly at a higher risk of quinolone-induced cognitive impairment, possibly due to declining renal function. One specific neuropsychiatric condition that involves cognitive impairment is delirium, a syndrome with an acute onset and fluctuating course. Risk factors include prior cognitive impairment, advanced age, infection(s), and exposure to some medications.^{20,21}

Ciprofloxacin and levofloxacin are the most widely used agents in the class of quinolones. The second most common adverse drug reactions (ADRs) of quinolone antibiotics are neurological ADRs. Mild neurological ADRs include dizziness, headache, somnolence, and insomnia. Less common, but more severe neuropsychiatric ADRs include confusion, delirium, and psychosis.²²

A review of psychiatric and neurological adverse reactions caused by quinolone antibiotics found eight cases of acute psychosis¹⁻⁸ induced by ciprofloxacin (seven in English, one in Spanish) and eight cases of delirium⁹⁻¹⁶ induced by ciprofloxacin, pefloxacin, and levofloxacin. These cases were among the most commonly reported neuropsychiatric adverse events caused by quinolone antibiotics. In most cases, the adverse events developed within a few minutes or during the first one to eight days of treatment. Some patients recovered within one day following drug withdrawal. The majority of patients with quinolone-induced delirium or psychosis had no underlying conditions or concomitant medications that could have resulted in the development of delirium or psychosis.²²

In a case of cognitive impairment, Kiangkitiwan and colleagues reported a case report of levofloxacin-induced changes with similarities to the patient in this case report. As with our patient, baseline cognitive functioning was achieved with quinolone discontinuation.²³

Although neuropsychiatric ADRs of quinolones, such as delirium and psychosis, are reported to be rare, accounting for <0.5% of the adverse reactions to quinolone antibiotics,²⁴ they are serious, affecting brain function. The exact mechanism behind quinolone-induced delirium is unclear, but the underlying mechanism is suspected to involve GABA inhibition.

These neuropsychiatric ADRs appear to be dose-dependent and directly related to quinolone concentration at the receptor site.²² Risk factors for developing adverse events involving the central nervous system (CNS) include renal insufficiency, underlying disease of the CNS, and increased CNS penetration of the drug.²³

Physiological changes that occur with increased age, such as declining renal function, make elderly patients more prone to the development of quinolone-induced delirium and psychosis. Many quinolone antibiotics are renally eliminated (including ciprofloxacin and levofloxacin) and their neuropsychiatric ADRs appear to be concentration dependent. Therefore, these antibiotics should be used with caution in the elderly with reduced renal function.²²

Overall, quinolone-induced ADRs appear to be more frequently reported in adults aged 19 to 64 (57.2%) than older adults aged 65 and over (31.7%).²² Although it may appear that quinolone-induced ADRs happen less often in the elderly, it is important to note that signs of CNS adverse reactions such as confusion, weakness, loss of appetite, and tremors are often attributed to old age and go unreported.²⁵ Though there are different proposed mechanisms behind these neuropsychiatric ADRs, one proposed mechanism in particular,

increased quinolone concentration at the receptor sites, puts older adults at an increased risk of developing neuropsychiatric ADRs due to declining renal function. Thus, renally eliminated quinolone antibiotics, such as ciprofloxacin and levofloxacin, should be used with caution in older adults.^{22,23}

Conclusion

Identifying a suspected medication-related effect in a cognitively impaired patient is challenging, especially if baseline functioning abilities are not known. When abrupt onset cognitive changes are noted, medication-induced changes must be considered, particularly when medications are added or dosages are increased. Medical conditions, including infectious processes, are also common reasons for cognitive changes. Recognizing that some agents used to treat those infections are associated with cognitive impairment, is critically important.

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