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Case Report

Ciprofloxacin-Induced Psychosis with Pseudobulbar Affect in A Patient with End-Stage Renal Disease

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Abstract

New-onset psychosis in mid to late life is an interesting and uncommon phenomenon. Typically, onset of psychosis is during adolescence. Earlier manifestations (childhood) and later manifestations (after 45 years old) are rare, as men tend to be diagnosed between 18 - 25 and women between 25 - 35 (albeit with a second peak noted near menopause). Clinicians should be wary when new psychotic symptoms develop in a patient outside of these peak times, as psychiatric diagnoses often follow a patient lifelong, prompting treatment with chronic medications that carry a risk of significant side effects. Below, I present a case of new-onset psychosis and pseudobulbar affect (PBA) secondary to ciprofloxacin that without prudent investigation may have ended up receiving inpatient psychiatric treatment and chronic psychotropic medication for a chronic psychiatric condition she did not ultimately have. The complication of PBA is one that has not yet, to my knowledge, been documented in the literature to date.

Keywords: Ciprofloxacin; Psychosis; Pseudobulbar; Fluoroquinolone

Case Report

A 52-year-old black female with end-stage renal disease (ESRD) secondary to poorly-controlled hypertension and chronic nonsteroidal anti-inflammatory drug (NSAID) use was admitted to the internal medicine service with acute onset of delusions, paranoia, and visual hallucinations. A week prior to her arrival, she had presented to an outside hospital with a headache and profound hypertension. At that time, she was of her normal state of mind. Her blood pressure was brought under control, and she had a peritoneal catheter surgically placed to initiate dialysis for her ESRD. She tolerated the procedure well. One of two blood cultures returned positive for *Escherichia Coli*, and the patient was started on cefepime due to concern for bacteremia. When antibiotic sensitivities resulted with resistance to cefepime, the patient was converted to meropenem. She was transitioned to ciprofloxacin 500mg daily by mouth on the day of discharge.

The following day she presented to our hospital where she was noted to have had a "mental breakdown" per her family, as she was totally unlike herself. She had paranoid delusions of her family trying to kill her and vivid hallucinations of angels that would only save people of certain blood types. Furthermore, she seemed to be responding to internal stimuli. She exhibited "emotional incontinence" as described by the attending psychiatric physician, exemplified by odd, poorly-timed laughter and bouts of inappropriate tearfulness which was entirely out of her control. She had never experienced similar symptoms, and her family was gravely concerned.

Initial workup revealed no obvious medical or neurologic causes. Neurologic exam was notable only for a tremor of the left upper extremity in the context of general tremulousness. Her memory, attention, and orientation were intact. She did have profound hyper-

tension upon arrival (210/111 mmHg) with mild sinus tachycardia as evidenced by ECG, but this was controlled throughout the rest of her stay with systolic blood pressures ranging from the 120s to 170s. A complete battery of labs were sent. A complete metabolic panel yielded a potassium of 5.1, CO_2 of 21 with an anion gap of 20, BUN of 79, and creatinine of 9.26 with a phosphorus of 6. Her complete blood count was notable only for a mild anemia to 10.3 g/dL. Testing was within normal limits or negative for HIV, syphilis, blood cultures, urine toxicology screen (aside from opiates which had been used for pain in the recent past), thyroid-stimulating hormone, Vitamin B12, folate, and ammonia. She had no urinary tract infection on urinalysis. Imaging revealed a normal CT scan of her head as well as unremarkable MRI Brain without contrast. A routine EEG was also negative for seizure activity. Chest X-Ray showed a mildly enlarged cardiac silhouette, but was otherwise unremarkable.

She was provisionally diagnosed with "unspecified psychosis" and "pseudobulbar affect" due to her hallucinations, delusions, and inappropriately intense, uncontrollable affect. From a psychiatric standpoint, the patient was placed under one-to-one observation for safety, and plans to transfer her to an inpatient psychiatric facility were initiated. On my chart review as part of the consulting neurology team, I made a few interesting discoveries. First, the patient had been started on ciprofloxacin a day prior to her symptom onset. Second, the dose had been inadvertently increased upon her admission to 500mg twice daily, double the maximum dose recommended for patients with ESRD. We made a recommendation to the primary team to discontinue the ciprofloxacin after a literature review confirmed prior case reports of fluoroquinolone-induced psychosis. The primary team then began holding her ciprofloxacin doses that same day.

Within two days, the patient already demonstrated a marked improvement in her symptoms without any psychotropic medications. She exhibited a more appropriate affect, with only two brief episodes of inappropriate laughter in a ten-minute discussion. She imparted that her visual hallucinations had abated. By the fourth day after cessation of ciprofloxacin, she had a thorough discussion with our team where she exhibited clear insight and relayed what she had experienced concerning visual hallucinations. She was self-conscious about her prior predisposition toward inappropriate laughter and tears. Per family, she was back to her pre-morbid baseline, and plans for inpatient psychiatric care were foregone. She had only received a one-time dose of olanzapine 2.5mg the evening prior to this conversation, but otherwise had not received any psychotropic medication during her stay.

The patient and her family were extremely relieved, and grateful for our precision and thoughtful care which prevented the patient from undergoing costly inpatient psychiatric care, chronic treatment with neuroleptic medication, and a primary psychiatric diagnosis which may have followed her in future care.

Discussion

The fluoroquinolones are a commonly used class of antibiotic medications that function by inhibition of type II isomerases DNA Gyrase and topoisomerase IV used in bacterial synthesis. Ciprofloxacin is one of the fluoroquinolones. It generally exhibits an oral bioavailability of 70%, but in healthy adults approximately only 10% of the plasma dose reaches the cerebrospinal fluid (CSF). The fluoroquinolones have a well-known set of adverse drug reactions (ADRs). Central Nervous System (CNS) ADRs are reported in 1 - 2% of patients taking ciprofloxacin. However, these generally include dizziness, headache, insomnia, or somnolence [1]. In contrast, a large, five-year retrospective study showed that psychiatric ADRs only occurred in 0.015% of patients on ciprofloxacin [2]. Fluoroquinolone-induced psychosis is a known but rare entity. Of the fluoroquinolones, ciprofloxacin and ofloxacin are the most commonly-reported offenders [3]. The mechanism of action for these observed neuropsychiatric effects is unclear, but may be related to the gamma-Aminobutyric acid (GABA) -displacing properties of the quinolones due to their structural similarity of the GABA neurotransmitter. One pharmacologic study suggested that GABA-receptor antagonism may be an underlying cause of the CNS adverse reactions of the fluoroquinolones [4]. Indeed, fluoroquinolones have been showed to be epileptogenic [1]. There have been several reports of ciprofloxacin-induced mania as well as movement disorders. Attempting to elicit clues as to the mechanism of the CNS ADRs of fluoroquinolones, one study looked at positron emission tomography (PET) scans of the brain in these patients, but unfortunately gave no hints, as their findings showed no change to cerebral glucose metabolism, blood flow, or oxygen uptake [5].

When looking collectively at the existing case reports for ciprofloxacin-induced psychosis, onset of symptoms tended to begin early after medication administration, spanning from as soon as the second dose to as late as the eighth day of treatment [6-10].

Upon cessation of the offending medication, resolution of symptoms was also rapid, ranging from twelve hours to four days later. Case severity ranged from mild to severe psychosis, with one man who fled his home because he believed he had murdered his wife and son and that the police were going to hunt him down and kill him. He stole a police car and was only caught when he contacted other government agencies to "save him from the police" [9]. Importantly for this case, there have been links shown between ciprofloxacin-related neuropsychiatric manifestations and renal failure [1]. In addition, this patient had a recent surgery which may have predisposed her to a pro-inflammatory state, thus creating greater permeability of the blood-brain barrier. There is suggestion of an increased risk of CNS ADRs while concomitantly taking NSAIDs or theophylline. Furthermore, the neuropsychiatric ADRs have been interestingly shown to exhibit a dose response. A literature search revealed no results for association between fluoroquinolones and pseudobulbar symptoms, suggesting that this may be the first reported case of pseudobulbar affect related to ciprofloxacin administration.

For the patient examined in this case report, she had several risk factors for a CNS ADR to ciprofloxacin including ESRD, chronic NSAID use, and a likely pro-inflammatory post-surgical state. Within one day of beginning ciprofloxacin she had developed profound psychosis and pseudobulbar affect. (Table 1) Given the acuity of her symptoms coupled with this medication change, we hypothesized ciprofloxacin to be the culprit. After holding this medication, her symptoms improved within the next few days, and changed the trajectory and ultimate course of her inpatient stay.

Ciprofloxacin-induced psychosis is a phenomenon that is becoming better-documented in the medical literature. For patients outside of peak onset periods for primary psychosis it is vital to dissect the patient's recent history. Important considerations in these cases include the patient's medical history, new medications or changes to dosing, and any other temporally-relevant events that could better explain these acute changes. In the case in question, this careful investigation yielded a causative agent in ciprofloxacin. Fortunately, in these cases patients seem to improve spontaneously with the removal of ciprofloxacin. There are several medication interactions and comorbidities that influence the course of symptoms and their resolution. It is important that physicians evaluate their patients' medication regimens including dose adjustments for kidney or liver failure. Finally, a good literature review can help provide evidence of a suspected condition, particularly in uncommon or rare presentations. In implementing the "non-maleficence" pillar of medical ethics, it is in the best interest of both the patient and provider to ensure the appropriate diagnosis is discovered to avoid inappropriate, costly, and time-consuming care that may ultimately harm the patient.

Day	Relevant Clinical Events
1	The patient presented to an outside hospital with a headache in the context of profound hypertension and was admitted.
3	*Escherichia Coli* was found in one of two blood cultures. Cefepime treatment was started for presumptive bacteremia.
6	A peritoneal dialysis catheter was surgically placed for treatment of end stage renal disease.
7	Cefepime was transitioned to meropenem due to the sensitivity and susceptibility profile of the target organism.
8	The patient requested to leave the hospital, and was transitioned to ciprofloxacin 500mg PO daily prior to discharge.
9	The patient presented to our institution in the emergency department with insomnia, delusions, visual hallucinations, and pseudobulbar affect. Her ciprofloxacin was increased to 500mg PO twice daily via her primary team.
10	Psychiatry and Neurology were consulted.
11	Neurology recommended stopping Ciprofloxacin. The primary team began holding the medication.
13	The patient was notably improved. She was "feeling much better". Her affect was noted to be more appropriate, even with the introduction of humorous or emotional material.
14	The patient received a one-time dose of olanzapine 2.5mg PO at bedtime per psychiatry.
15	The patient participated in a thorough discussion about her prior hallucinations. She described them as "dark figures" and reported having not seen them in "a few days". She was self-conscious about her previously labile affect. She had "great insight" into her condition. Routine EEG returned with a normal read, and neurology signed off given her rapid and complete resolution of symptoms. Psychiatry (which had initially thought the patient would need an inpatient level of psychiatric care and had been placed on a 1:1 sitter) was impressed with the patient's improvement and eventually signed off.

Table 1

Acknowledgments

None.

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