Ciprofloxacin-Induced Renal Failure

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Abstract

Acute renal failure (ARF) is a common diagnosis in hospitalized patients, particularly in intensive care units (ICU). Determining the cause and contributing factors associated with ARF is crucial during treatment. The etiology is complex, and several factors often contribute to its development. Medications can cause acute tubular necrosis, acute interstitial nephritis, and crystal-induced or post-obstructive nephropathy. There have been several case reports of ARF secondary to fluoroquinolones. Here we report the development of acute renal failure within a few days of initiating oral ciprofloxacin therapy and briefly describe the different types of renal failure secondary to fluoroquinolone administration. Clinical studies demonstrate that using fluoroquinolones with other potentially nephrotoxic medications requires monitoring of renal function to limit the renal toxicity with these medications. Also, the risk-benefit profile of patients requiring fluoroquinolones should be considered.

Key words: Ciprofloxacin, renal failure, dialysis, antibiotic, acute kidney injury, fluoroquinolone

Introduction

Acute renal failure (ARF) is common in hospitalized patients, particularly in intensive care units (ICU). The estimated incidence of ARF in ICU patients ranges from 20 to 50%.[1] Determining the cause and contributing factors related to a patient's ARF is crucial during treatment. The classification of ARF can be divided into three broad categories: pre-renal, intrinsic renal, and post-renal. These categories include hypovolemia, congestive heart failure, drugs that impair renal autoregulation, severe sepsis with multiorgan failure, myoglobinuria, surgery, circulatory shock, nephrotoxic medications, papillary necrosis, retroperitoneal masses, urethral strictures, and prostatic hypertrophy.[2] This discussion will focus on medications as a cause of ARF. Medications can cause ARF through acute tubular necrosis (ATN) and acute interstitial nephritis (AIN).[2] There have been several case reports of ARF secondary to fluoroquinolone ingestion.[3] Here we report the development of acute renal failure within a few days of initiating oral ciprofloxacin therapy.

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Case

The patient is an 81-year-old African-American woman with a past medical history of interstitial

lung disease, type 2 diabetes, cervical spine fusion, dyslipidemia, Sjogren's disease with sicca syndrome, and obesity who initially presented to the emergency room complaining of acute abdominal pain and weakness. She had mild acute kidney injury with a blood urea nitrogen (BUN) of 14 mg/dL and a creatinine (Cr) of 1.1 mg/dL, up from her baseline BUN/Cr of 18/0.8 mg/dL. Her urinalysis was positive for 3+ bacteria, moderate blood, and 10 white blood cells/hpf, consistent with an acute urinary tract infection (UTI). She also had an altered mental status secondary to her infection. Computed tomography of the abdomen did not reveal any abnormalities. She was initially treated for three days with intravenous ceftriaxone and then oral ciprofloxacin 500 mg twice daily. The patient was discharged home to continue ciprofloxacin for two weeks. A list of her discharge medications are listed in Table 1. Of note, the patient was discharged on pravastatin, lisinopril, and furosemide which she had been taking prior to and during her admission.

Five days after completing the antibiotics the patient was brought to the hospital by ambulance after being discovered confused and lethargic. She had significant acute renal failure with a BUN/Cr of 75/11 mg/dL up from 10/0.8 mg/dL on her previous hospital discharge. She had hyperkalemia (potassium 6.3 mEq/L) and metabolic acidosis. Her urinalysis included 4+ yeast, trace bacteria, large blood, large leukocyte esterase, and numerous white blood cells. No urine eosinophils were seen, and the urine pH was 5. Intravenous antibiotics adjusted for renal function and intravenous fluids were started. A renal ultrasound was negative for renal abnormalities. A Quinton cath-

Table 1: Discharge medications

Plaquenil Sulfate 200 mg oral tablet: 1 tab, PO, Daily, 180 tab
pilocarpine 5 mg oral tablet: 1 tab, PO, TID, 90 tab
pravastatin 40 mg oral tablet: 1 tab, PO, Daily, 90 tab
Lyrica 75 mg oral capsule: 1 cap, PO, BID, 60 tab
Pepcid 20 mg oral tablet: 1 tab, PO, Daily, 180 tab
Levemir 100 units/mL subcutaneous solution: 42 units, subcut, Daily, Inject 42 units SQ daily, 3 mL
LORazepam 0.5 mg oral tablet: 1 tab, PO, TID, 90 tab
Cymbalta 60 mg oral delayed release capsule: 1 cap, PO, BID, 60 tab
predniSONE 5 mg oral delayed release tablet: 1 tab, PO, Daily, 1 ea
OxyCONTIN 40 mg oral tablet, extended release: 1 tab, PO, q12h, 60 tab
zolpidem 10 mg oral tablet: 1 tab, PO, Nightly, 30 tab, PRN: for sleep
metoprolol succinate 25 mg oral tablet, extended release: 1 tab, PO, Daily, 90 tab
potassium chloride 10 mEq oral capsule, extended release: 1 cap, PO, BID, 180 cap
furosemide (Lasix) 80 mg oral tablet: 0.5 tab, PO, BID, 30 tab
lisinopril 10 mg oral tablet: 1 tab, PO, Daily, 90 tab
amLODIPine: 5 mg, PO, Daily, 1 ea
niacin 50 mg oral tablet: 1 tab, PO, Daily, 30 tab
HYDROcodone-acetaminophen 10 mg-325 mg oral tablet: 1 tab, PO, q4h, 24 tab, PRN: for pain
ciprofloxacin 500 mg oral tablet: 1 tab, PO, BID, 10 tab,

eter was placed, and the patient had hemodialysis (HD) on day one of admission. The patient was later started on fluconazole, and antibiotics were discontinued since as her urine culture was positive only for yeast. Her creatinine kinase (CK) was greater than 3500 IU/L on admission. She was diagnosed with acute tubular necrosis secondary to ciprofloxacin, which was exacerbated by her UTI and an elevated CK. Her CK levels, renal function, and urine output slowly improved over eleven days after withdrawal of the ciprofloxacin and HD (see Figures 1 and 2), and she was discharged to a skilled nursing facility with BUN/Cr levels near her baseline.

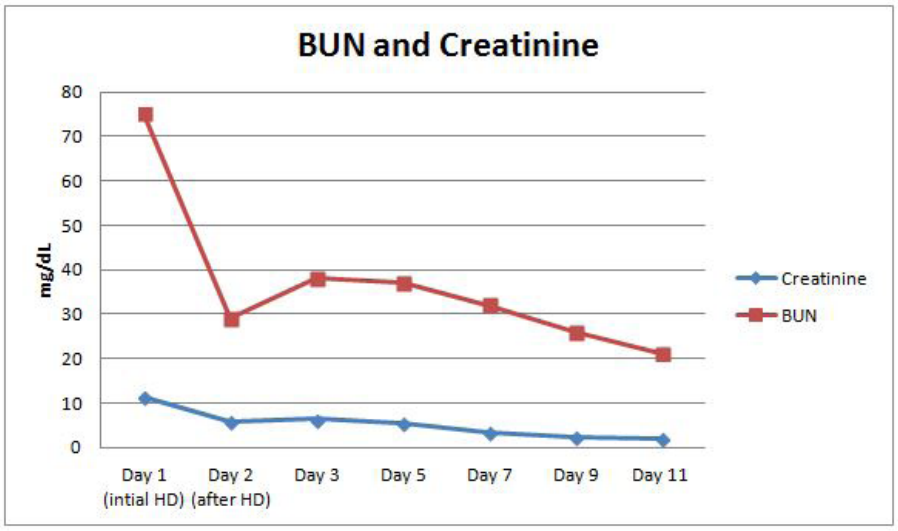

Figure1

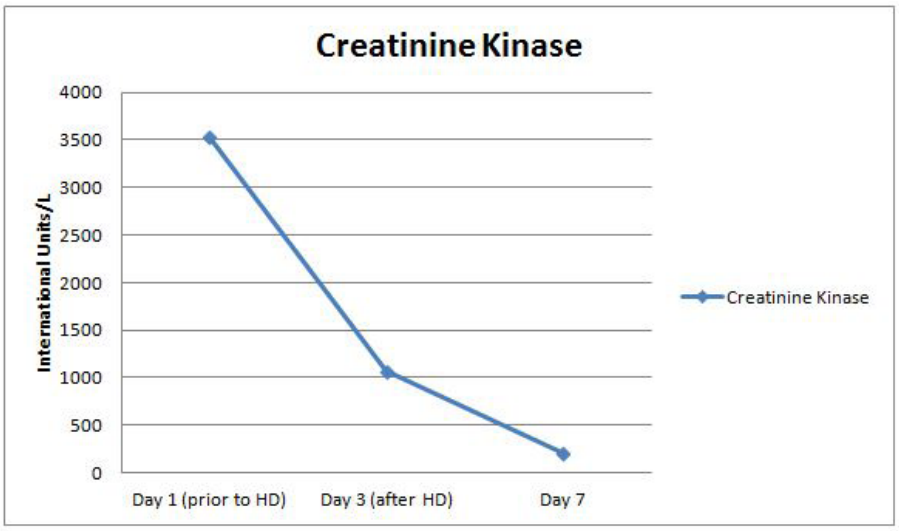

Figure 2

Table 2: Summary of potential causes of ARF secondary to ciprofloxacin administration

Acute interstitial nephritis	• Lab findings generally non-specific • Lab findings - Proteinuria - Hematuria - Eosinophiluria - Pyuria - Eosinophilia - Renal failure • Clinical symptoms - Acute arthralgia - Skin rashes - Fever - Flank pain • Recent use of nephrotoxic medication • Increased risk with administration of other nephrotoxic medications • Usually no need for renal biopsy
Rhabdomyolysis and myoglobin induced renal failure	• Lab findings - Elevated serum creatinine kinase - Renal failure - Myoglobinuria - Hyperphosphatemia - Hyperkalemia - Hypocalcemia • Complications involving tendon, cartilage, bone, and muscle • Secondary to chelation of magnesium and generation of reactive oxygen species • Usually involves multiple drug-drug interactions
Crystal induced nephropathy	• Occurs with medications dependent on urine pH for solubility and excretion • Typically occurs with urine pH greater than 6.8 • Examination of urine sediment with polarizer is sufficient to diagnose without renal biopsy
Acute tubular necrosis	• Develops with prolonged renal hypoperfusion • Drugs can also cause direct toxicity to renal tubular cells • Muddy brown casts are seen on examination of urine sediment • Renal failure is present

Discussion

There have been several case reports of patients with ciprofloxacin-induced renal failure. The causes of ARF in these patients include crystal-induced nephropathy, ATN, AIN, allergic interstitial nephritis, and myoglobin-induced renal failure. These patients have had several comorbidities and infections ranging from cystic fibrosis exacerbations to mycobacterial infection to uncomplicated UTIs. One case report describing ciprofloxacin nephropathy emphasized potential risk factors for this complication; these included increased age, low body mass, and co-ingestion of other potentially nephrotoxic medications.[4] It was previously reported that fluoroquinolones could cause acute renal failure after ingestion of large quantities, but it is now recognized that therapeutic doses of fluoroquinolones can also cause renal injury. The potential causes of ARF secondary to ciprofloxacin administration are discussed briefly below, and a summary is provided in Table 2.

Acute interstitial nephritis iagnosis

Typically AIN secondary to fluoroquinolones develops within hours to weeks in patients with pre-existing renal disease. An elevation in serum Cr from a patient's baseline is the most obvious finding as other laboratory findings and clinical manifestations are non-specific. The co-administration of other potentially nephrotoxic medications increases the risk of AIN.[5] Allergic interstitial nephritis is a subtype of AIN. It is the most common cause of fluoroquinolone nephrotoxicity and is secondary to a type III hypersensitivity reaction.[5] The identification of this cause of renal failure is often difficult and can go undiagnosed since these patients rarely develop oliguria and are commonly taking other potentially nephrotoxic medications concomitantly. The clinical presentation can include acute arthralgia, eosinophilia, eosinophiluria, fever, skin rashes, proteinuria, hematuria, pyuria, flank pain, and renal failure.[5] A recent exposure to a potentially nephrotoxic medication and improvement of renal function after discontinuation of this medication are often adequate for a diagnosis, precluding the need for a kidney biopsy.

Rhabdomyolysis and myoglobin-induced renal failure

Drug toxicity has become an important cause of nontraumatic rhabdomyolysis, and fluoroquinolones can cause a spectrum of musculoskeletal complications involving tendon, cartilage, bone, and muscle.[6] Apart from tendinopathy, the fluoroquinolone antibiotics, including ofloxacin, norfloxacin, and levofloxacin, have been implicated in rhabdomyolysis.[7] The musculoskeletal toxicity seems to be related to chelation of magnesium, inhibition of the mitogen-activated protein kinase (MAPK) signaling pathway, and activation of reactive oxygen species. Also, the fluorine atom in the fluoroquinolone molecule has been implicated in myotoxicity.[6] As in all cases of drug-induced rhabdomyolysis, discontinuation of the drug is mandatory.[7] Most myotoxic events are not due to single drugs but to drug–drug interactions. The most prominent and clinically relevant examples are any combinations of statins, fenofibrates, cyclosporine, and protease inhibitors. Some muscle injury could be avoided by prudent drug choice and dose adjustments.[7]

Crystal-induced nephropathy

Crystal nephropathy may occur with medications that depend on urine pH for solubility and excretion.[8] Some of the more commonly recognized drugs associated with crystal-induced renal insufficiency are acyclovir, sulfonamides, and methotrexate.[9] Ciprofloxacin has been reported as a rare cause of crystal nephropathy, along with aspirin, ampicillin, cephalexin and other commonly prescribed medications.[9] Ciprofloxacin-induced crystalluria typically occurs in alkaline urine (pH greater than 6.8) but can occur with more acidic urine.[4] At a neutral or alkaline pH, ciprofloxacin is poorly soluble, resulting in crystallization within the tubules and development of obstructive nephropathy.[10] Most cases of ciprofloxacin-induced renal failure have occurred in older patients with pre-existing renal disease or with high doses of

the medication, but it can occur in young, healthy patients using therapeutic doses of the medication. When performed reasonably close to ingestion, examination of urine sediment using a polarizing microscope should be sufficient to diagnose ciprofloxacin crystal nephropathy without needing a renal biopsy.[4]

Acute tubular necrosis

ATN, along with pre-renal azotemia, accounts for more than half of the cases of renal failure seen in hospitalized patients.[11] In healthy patients, the kidney responds to a drop in perfusion pressure by maintaining normal blood flow and glomerular filtration rate by autoregulation mechanisms. When these mechanisms are disrupted, acute renal failure secondary to ATN and pre-renal azotemia can occur. Once the renal perfusion pressure drops below the autoregulatory range, the afferent arteriole resistance increases, leading first to pre-renal azotemia and later to ATN if the duration of ischemia is prolonged.[11] This leads to necrosis and apoptosis of renal epithelial cells, which eventually slough off and form urinary casts. This debris can obstruct tubules and later an inflammatory cascade is activated that leads to more kidney damage. ATN can occur even in normotensive patients in the presence of medications that affect autoregulation, leading to renal hypoperfusion.[11] These medications include angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, COX-2 inhibitors, and NSAIDs.[11] Ciprofloxacin and other fluoroquinolones have been recognized as potential nephrotoxic medications, causing direct toxicity to renal cells, leading to the development of ATN. One case series reported plasma ciprofloxacin levels were seven-fold higher than the usual therapeutic concentration in a patient that developed ATN secondary to ciprofloxacin ingestion.[10] Other conditions can increase susceptibility to renal hypoperfusion and include increasing age, atherosclerosis, chronic hypertension, CKD, sepsis, hypercalcemia, hepatorenal syndrome, and intravenous contrast.[11] It is important to review the patient's medication list when prescribing new medications to avoid deleterious effects on renal function and schedule serial lab tests for renal function.

High risk patients

Severe volume contraction is the most important risk factors for crystal deposition within the kidneys. Volume contraction and a decrease in the effective circulating volume occur in patients with chronic diarrhea, anorexia, vomiting, severe sepsis, congestive heart failure, and other less common causes.[9] These are common conditions seen in hospitalized and even some non-hospitalized patients. The risk of intratubular crystal deposition increases in these patients because of prolonged contact of the medication with renal tubules[9] as a result of decreased flow through the kidneys. Underlying renal impairment is also a risk factor for developing medication-induced renal failure.[4, 8, 9] This likely results from increased exposure of the kidney to greater concentrations of the medications.[9] This highlights the importance of adjusting medication dosage based upon renal function in an attempt to prevent this complication.

Prevention of ciprofloxacin-induced renal failure

Because the exact mechanisms of all causes of ciprofloxacin-induced renal failure are not fully elucidated, only general recommendations can be made regarding the prevention of this complication. The dose of ciprofloxacin based upon a patient's renal function should be adjusted at the time of prescription. Adequate hydration during therapy with ciprofloxacin can help

prevent crystalluria and associated renal toxicity. Monitoring of renal and liver function during prolonged treatment is important since prolonged treatment can cause liver dysfunction in addition to renal dysfunction, especially in patients with previous liver damage.

Conclusion

Our patient had many of the characteristics identified as potential risk factors for the complication of ARF secondary to a fluoroquinolone, including increased age, risk factors for the development of atherosclerosis, and chronic medications affecting renal autoregulation. She was also taking a statin medication, possibly compounding the potential myotoxicity of ciprofloxacin and the risk of acute renal failure secondary to rhabdomyolysis. The combination of these factors, in addition to therapeutically dosed ciprofloxacin, led to the development of her acute renal failure. The use of fluoroquinolones with other potentially nephrotoxic medications should prompt monitoring of renal function. Also, the risk-benefit profile of treatment with fluoroquinolones should be considered in all patients.

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