Fluoroquinolone-Induced Acute Interstitial Nephritis: Two Case Reports

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Acute interstitial nephritis is a disease affecting the renal tubules and interstitium.[1] It is thought to occur secondary to an allergic hypersensitivity reaction.[1] The clinical presentation is variable and nonspecific, and may include fever, maculopapular rash, arthralgia, edema, hypertension, eosinophilia, eosinophiluria, pyuria, hematuria, proteinuria, oliguria, leukocytosis, elevation of serum immunoglobulin E, hyperkalemia, and acidosis.[1,2] Acute interstitial nephritis can have an infectious, inflammatory, or drug-related cause.[2]

Numerous drugs have been implicated in acute interstitial nephritis, some of which include nonsteroidal anti-inflammatory drugs, diuretics, anticonvulsants, allopurinol, and antibiotics.[2-4] Fluoroquinolones are commonly used antibiotics that are thought to be relatively nontoxic.[5] However, the potential exists for these agents to cause substantial morbidity, as illustrated by published reports of fluoroquinolone-induced acute interstitial nephritis.[6-25] Ciprofloxacin accounts for the majority of these cases,[6-22] with just a few reports for norfloxacin.[10,23,24] A MEDLINE search for January 1966 to December 2001 yielded only one published report of acute interstitial nephritis secondary to levofloxacin, a newer fluoroquinolone.[25]

Two cases of fluoroquinolone-induced acute interstitial nephritis are reported here, one due to norfloxacin and the other to levofloxacin. As the use of this class of anti-infectives increases and as new members of the class are introduced, it is important that pharmacists be aware of the growing evidence of this clinically important adverse effect.

CASE REPORTS

Case 1

A 70-year-old woman with primary pulmonary hypertension was admitted to the respirology service for persistent and increasing nausea accompanied by occasional vomiting and anorexia over a 2-week period, which had resulted in a 4.5-kg weight loss. Headaches occasionally accompanied the nausea.

Her medical history included New York Heart Association class IV primary pulmonary hypertension, hypothyroidism, a 2-year history of intermittent nausea, and recurrent urinary tract infections, for which she had previously received norfloxacin. She had a remote history of cholecystectomy and hysterectomy.

The patient was reportedly allergic to sulfa drugs. The family and social histories were unremarkable.

Her medications used at home included epoprostenol (by infusion), diltiazem, amiloride, furosemide, warfarin, a potassium supplement, levothyroxine, omeprazole, tolterodine, dimenhydrinate, acetaminophen with codeine, vitamin E, glucosamine, and oxygen. At the time of admission, she was on day 9 of treatment with norfloxacin 400 mg PO bid.

On physical examination, the patient's heart rate was 100 beats/min, blood pressure 106/52 mm Hg, respiratory rate 24 breaths/min, and temperature 36.2°C. Her face and upper torso appeared flushed, consistent with epoprostenol therapy. Jugular venous pressure was elevated, and mild pedal edema was

noted. Cardiac examination revealed a right ventricular heave, hard pulmonic component of S2, and a grade III/VI diastolic murmur.

Laboratory investigations revealed serum creatinine 193 µmol/L (normal range 55 to 115 µmol/L) and blood urea nitrogen 15.2 mmol/L (normal range 2.5 to 7.0 mmol/L). Two months earlier, serum creatinine and blood urea nitrogen had been 91 µmol/L and 7.8 mmol/L respectively. Other abnormalities included sodium 132 mmol/L (normal range 135 to 145 mmol/L), potassium 5.4 mmol/L (normal range 3.5 to 5.0 mmol/L), bicarbonate 17 mmol/L (normal range 24 to 32 mmol/L), albumin 28 g/L (normal range 35 to 50 g/L), total serum amylase 33 U/L (normal range 36 to 128 U/L), international normalized ratio (INR) 4.0 (normal range 2.0 to 3.0), and partial thromboplastin time 66 s (normal range 28 to 38 s). The platelet count was 81 x 10^9/L (normal range 150 to 400 x 10^9/L), which, although below normal, was consistent with previous records for this patient.

Electrocardiography showed a right bundle branch block and T-wave abnormalities.

The substantially worsening and debilitating nausea that had necessitated admission to hospital was thought to be due to the use, over the 9 days before admission, of unadjusted doses of norfloxacin in the setting of renal failure. Hence, the norfloxacin was discontinued on day 3 of the hospital stay (for a total duration of treatment of 12 days); the nausea subsequently diminished.

Several studies were undertaken to investigate the acute renal compromise. Urinalysis showed below-normal sodium and osmolality, minimal hematuria consistent with an INR of 4.0 or acute interstitial nephritis (or both), trace proteinuria, and eosinophils. Renal ultrasonography revealed no obstruction. On day 10 of the hospital stay (7 days after discontinuation of norfloxacin), acute interstitial nephritis secondary to norfloxacin was diagnosed, and prednisone 40 mg PO daily was initiated. The patient was discharged on day 14, at which time she was asymptomatic (serum creatinine 185 µmol/L and blood urea nitrogen 22 mmol/L). Upon follow-up 12 days after discharge, serum creatinine and blood urea nitrogen had decreased to 109 µmol/L and 11.5 mmol/L respectively.

Case 2

A 44-year-old woman was admitted to the authors' institution for assessment of severe pulmonary arterial hypertension and pericardial effusion in the setting of mixed connective tissue disease.

The patient had a 3-week history of shortness of breath and a continuous cough, accompanied by an increase in the volume of her usual white sputum. She reported sharp, burning retrosternal chest pain and had had several episodes of nausea and vomiting. Her family physician prescribed azithromycin, which had provided only minimal relief. Levofloxacin was then prescribed and had been taken for 6 days before admission. She had become increasingly short of breath, and her cough and chest pain had worsened. She was admitted to another hospital in the region, where severe pulmonary hypertension, possible pneumonia, and renal failure were diagnosed. She was treated for 1 day with methylprednisolone and levofloxacin before being transferred to the authors' hospital.

Her medical history was significant for an overlap connective tissue disorder with features of CREST (calcinosis, Raynaud's, esophagus, sclerodactyly, telangiectasia) syndrome and mixed connective tissue disease, as well as for cardiomegaly and hypothyroidism. She had experienced an episode of pneumonia approximately 6 months previously.

She was allergic to IV pyelography dye; the allergy manifested as urticaria, pruritis, and fever.

Upon admission to the authors' facility, the patient had been taking levofloxacin 500 mg PO daily for 7 days, as well as omeprazole, fluticasone, and salbutamol (the latter 2 drugs by inhaler).

The patient reported dizziness associated with postural changes, headache, chest pain, nausea and vomiting, prior observation of blood in her stool, occasional "muddy-colour" urine, bloody urine a few months before, severe flank pain occurring a few months previously that had radiated over her back and under her ribcage, and a recent weight gain of approximately 2 kg despite reduced dietary intake.

On examination, her heart rate was 96 beats/min, blood pressure 120/84 mm Hg without postural change, and respiratory rate 18 breaths/minute; she was afebrile. Jugular venous pressure was elevated, and she had bilateral increase in breath sounds, bilateral but equal decrease in tendon reflexes, tibial edema, and telangiectasia of the hands and face. The results of the remainder of the physical examination were unremarkable.

Abnormal laboratory findings included serum creatinine 195 µmol/L and blood urea nitrogen 17.2 mmol/L. Six months earlier, her serum creatinine had been 80 µmol/L. Other abnormalities included sodium 130 mmol/L, monocytes 1.0 x 10^9/L (normal range 0.2 to 0.8 x 10^9/L), reticulocyte distribution width

15.5 (normal range 12.0 to 15.0), and albumin 28 g/L. Urinalysis revealed urinary eosinophils and urinary protein of at least 3 g/L.

Chest radiography showed cardiomegaly and absence of pleural effusion. Electrocardiography showed sinus tachycardia at 100 beats/min, incomplete right bundle branch block, and a nonspecific flattening of T-waves at leads V1 to V3.

The acute compromise in renal function was presumed to be secondary to levofloxacin-induced acute interstitial nephritis, given the normal serum creatinine level 6 months earlier and the finding of eosinophils in the urine. Levofloxacin was discontinued on the third day of the hospital stay, for a total duration of therapy of 10 days. Prednisone 30 mg PO daily was initiated, and she was discharged on the 11th day of the hospital stay; at that time, serum creatinine was 165 µmol/L and blood urea nitrogen 10.2 mmol/L. Follow-up at 3 months revealed serum creatinine of 116 µmol/L and blood urea nitrogen of 7.6 mmol/L.

DISCUSSION

Several features of these 2 case reports are consistent with fluoroquinolone-induced acute interstitial nephritis, as reported in the literature. In each of these patients, the serum creatinine and blood urea nitrogen levels rose within 10 days of initiation of the offending agent. Most cases of drug-induced acute interstitial nephritis develop within 10 days, but the condition may develop within hours to weeks after initiation of therapy.[2-4] As well, urinary eosinophils and proteinuria were present in both of these patients.[2-4] Edema was present in both cases and hematuria in one of the cases[1-3]; however, it is unclear if other factors, specifically pulmonary hypertension and concomitant warfarin therapy, played a role in these observed abnormalities. With discontinuation of the fluoroquinolones, renal status improved and was approaching normal at follow-up appointments (23 days and approximately 3 months after discontinuation of norfloxacin and levofloxacin respectively). In most reported cases of fluoroquinolone-induced acute interstitial nephritis, renal function returns to normal or nearly normal over a period of days to months.[2,3,26] In contrast to the patients described here, fever and rash were noted in other published reports.[2-4,26] Flushing secondary to epoprostenol infusion might have impeded the ability to detect a rash in patient 1. It is noteworthy that both of these patients had pulmonary hypertension, a rare disease characterized by substantial morbidity and a high mortality rate.[27] The association, if any, between fluoroquinolone-induced acute interstitial nephritis and pulmonary hypertension is unknown.

In summary, pharmacists should be aware that several fluoroquinolones have been associated with acute interstitial nephritis, including ciprofloxacin, norfloxacin, and levofloxacin. Although ciprofloxacin is most often cited in connection with acute interstitial nephritis, this may simply represent prescribing patterns. Given that this adverse drug reaction occurs with several of the fluoroquinolones, it may be due to a class effect. The possibility of a class effect makes it essential that pharmacists be vigilant in monitoring for this adverse drug reaction with any dose of a fluoroquinolone.[26] Patients who experience acute interstitial nephritis caused by one fluoroquinolone should be considered susceptible to the others, given the substantial morbidity of the reaction. If renal insufficiency with features of acute interstitial nephritis occurs in the presence of a fluoroquinolone and other causes of renal insufficiency have been excluded, the fluoroquinolone should be promptly discontinued. Further management may include corticosteroid therapy; however, this strategy remains controversial.[2,4]

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