Pulmonary Toxicity with Fluoroquinolones
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Citation

Abstract
Adverse drug reactions associated with antimicrobials have become a topic of major importance and concern in the last few years. Fluoroquinolones are a group of interesting and at times unpredictable class of antimicrobial agents which are used extensively in clinical practice. Over the past 20 years, fluoroquinolones have demonstrated landmark safety profiles. Ciprofloxacin and levofloxacin remain two of the safest and best-tolerated fluoroquinolones over a wide range of doses. The most common drug-related adverse effects with fluoroquinolone therapy involve the gastrointestinal tract and central nervous system (1). Others include skin rashes, pruritis, photoallergic reactions, arthropathy, and tendinopathy, especially in patients younger than 30 years old. These adverse effects are usually transient and mild to moderate in severity, and rarely require discontinuation of therapy. However, serious toxic reactions have also been reported. We report two cases of hypersensitive pneumonitis with vasculitis followed exposure to ciprofloxacin and/or levofloxacin.

CASE 1
An 82-year old Caucasian Male was admitted with two weeks history of progressive dyspnea and peripheral edema associated with petechial skin rash. He has been treated as an in-patient for acute diverticulitis with intravenous ciprofloxacin and subsequently discharged on oral levofloxacin for seven days. The patient was evaluated in the emergency department (ED) two days later with dyspnea, mild lower extremities edema and a petechial skin rash involving all extremities and the torso. He was discharged home with a diagnosis of hypoalbuminemia and a possible allergic reaction to fluoroquinolones. The patient returned to ED ten days later with complaints of dyspnea on minimal exertion, worsening peripheral edema, proximal nocturnal dyspnea and orthopnea. His past medical history included atrial fibrillation, gout and hypertension. His out-patient medications included nadolol, coumadin, allopurinol, accupril and hydrochlorothiazide. The patient’s vital signs were significant for an oxygen saturation of 88% on room air, blood pressure of 89/48 mmHg, irregular heart rate of 84/min. Pulmonary examination revealed bilateral inspiratory rales (left side more than right side); cardiovascular exam showed irregular heart rate and 2+ lower extremities edema with a generalized petechial skin rash. Laboratory data on admission are outlined in Table 1.

Figure 1: Table 1 Lab data

A frontal chest radiograph revealed bilateral interstitial infiltrates (Figure 1).
The patient was admitted to the hospital with a diagnosis of congestive heart failure and vasculitis.

Following admission, the patient was diuresed effectively with improvement of lower extremities edema, but without a significant improvement of hypoxemia ($\text{SpO}_2$ 92% on 3 liters of nasal oxygen with de-saturation on exertion). A transthoracic echocardiogram revealed LVEF of 60% with diastolic dysfunction and normal valves. Serologic studies for autoimmune disease and hepatitis viruses were sent and results outlined in Table 2.

A diagnostic right heart catheterization was performed on hospital day twelve, which revealed a right atrial pressure of 13 mmHg, pulmonary artery pressure of 65/15 mmHg and oxygen saturation of 57%, and PCWP of 13 mmHg. A chest CT scan revealed bilateral alveolitis (Figure 2).

A diagnostic flexible bronchoscopy revealed no endobronchial lesions; Bronchoalveolar lavage (BAL) revealed bloody return with hemosiderin laden macrophages and cultures for TB, PCP, fungus, CMV and cytology were negative. Transbronchial biopsies of the left upper lobe, lingula, and left lower lobe revealed acute alveolitis with capillaritis and nonspecific interstitial thickening. The patient developed progressive hypoxemia, with CXR revealing increased bilateral alveolar infiltrates (Figure 3).

The patient was transferred to intensive care unit with a
diagnosis of diffuse alveolar hemorrhage (DAH) with type II respiratory failure. He was given with methylprednisolone 1 gm intravenously daily for three days and non-invasive ventilation with BIPAP and deferred anticoagulation. The patient’s hypoxemia resolved over forty-eight hours with SpO₂ of 94% on three liters oxygen along with a reduction in alveolar infiltrates. Patient was discharged home on a tapering dose of prednisone and three liters of nasal oxygen. The patient remained on three liters oxygen a month later despite complete resolution of lower extremity edema and the skin rash. A CT scan of chest revealed resolved pulmonary alveolitis and residual intestinal infiltrates in the lower lobes that persisted in CT scan 3 months later. Pulmonary function test revealed severe obstructive disease with decreased diffusion capacity. The patient was clinically stable at this time on three liters nasal oxygen and 7.5mg of prednisone daily.

The clinical presentation of cutaneous vasculitis and DAH with respiratory failure in setting of recent use of levofloxacin that responded to glucocorticoid therapy was considered to be consistent with hypersensitivity reaction to levofloxacin.

**CASE 2**

A 52-year old female, 30-pack year smoker without any past medical history not on any medications was evaluated with a 2-week history of unremitting high-grade fever and non-productive cough associated with moderate lower back pain and loss of appetite. There was no history of alcohol or drug abuse, high-risk sexual behavior, recent travel, or contact with sick pets or birds. She was seen in emergency department (ED) 2 days prior, and was treated for presumed bronchitis with oral ciprofloxacin. Her chest X ray at that time was normal. Two days later, the patient returned to the ED with persistent fever of 38.9°C, non-productive cough and generalized bilateral lymph-adenopathy involving the anterior and posterior cervical, supraclavicular and axillary lymph nodes that were non-tender and mobile. The right posterior cervical lymph nodes were tender, and measured 1.0x0.5 cm. Her vitals were significant for a temperature of 39°C, tachycardia and tachypnea without hypoxia. Her pulmonary examination was characterized by end inspiratory crackles at the lung bases. The remainder of her physical examination was unremarkable. Laboratory data on admission are outlined in table 3.

She was admitted to hospital for further evaluation of persistent fever, coughs and generalized lymph-adenopathy.

After admission to hospital, ciprofloxacin and acetaminophen were discontinued and blood and urine cultures were sent in addition to serologic studies for CMV, EBV, HIV, hepatitis A/B/C, Parvovirus B19 and toxoplasma; ANA titer, rheumatoid factor and SPEP. The patient continued to be febrile to 40.8°C and developed an itchy, macular rash involving all extremities and the trunk on hospital day 3. A CT scan of the neck, chest, abdomen and pelvis was obtained and confirmed the generalized lymph adenopathy (Figure 4 A,B and C).

**Table 3 Lab data on admission**

<table>
<thead>
<tr>
<th>Test</th>
<th>Lab data</th>
<th>Normal range</th>
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<tbody>
<tr>
<td>CBC and differential</td>
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<tr>
<td>Hemoglobin (g/dL)</td>
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<td>12-16</td>
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<td>Hematocrit (%)</td>
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<td>MCV (fL)</td>
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<td>MCH (pg)</td>
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<td>RDW (%)</td>
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<td>Eosinophil (%)</td>
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<tr>
<td>Liver Function Tests</td>
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<tr>
<td>Lactic Dehydrogenase (U/L)</td>
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<td>98-192</td>
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</table>

Figure 6

Figure 7

Figure 4A. CT of neck without contrast revealing bilateral enlarged lymph nodes in the posterior triangle and internal jugular vein (arrows)
Figure 8
Figure 4B. CT of chest with contrast revealing enlarged subcarinal and hilar lymph nodes (arrows).

Figure 9
Figure 4C-CT of abdomen with contrast revealing enlarged retroperitoneal lymph nodes (arrows)

On hospital day 5, the patient’s dyspnea and cough worsened with new bilateral basal interstitial infiltrates on CXR (Figure 5)

Figure 10
Figure 5- Bilateral Interstitial Infiltrates

Figure 11
Figure 6. Trends of temperature and laboratory data during hospitalization

There was and associated increase in WBC to 44.9 K/μL (8% eosinophils and 56% lymphocytes with moderate plasmacytoid cells) (Figure 6).

Flow cytometry of peripheral blood revealed a polyclonal plasmacytosis (10%) without evidence for abnormal myeloid maturation or lymphoproliferative disorders. A diagnostic flexible bronchoscopy revealed no endobronchial lesions. Bronchoalveolar lavage (BAL) was normal without eosinophilia and cultures for TB, PCP, fungus, CMV and cytology were negative. Transbronchial biopsies of the right lower lobe revealed nonspecific interstitial inflammation with chronic inflammatory cells without evidence of
An excision biopsy of the cervical lymph node was considered and deferred as the patient improved dramatically with resolution of fever and improved leukocytosis 10 days after presentation. The skin rash, generalized lymph adenopathy and WBC normalized soon thereafter. A follow up CT of chest and abdomen 2 weeks later were normal.

The clinical presentation of fever, rash, generalized lymphadenopathy, eosinophilia and nonspecific interstitial pneumonitis was thought to be most consistent with ciprofloxacin associated hypersensitivity reaction.

DISCUSSION

The primary mechanisms of antimicrobial toxicity include direct effects, hypersensitivity, changes in microbial flora, drug interactions and microbial lysis (2). Drug-related hypersensitivity is an idiosyncratic reaction involving activation of a pathogenic, drug-specific immune response (immediate reactions mediated by IgE or delayed-type reactions mediated by T cell). However, because of obvious difficulties in determining a cause in clinical practice, the term is generally used to describe adverse drug reactions with concurrent fever, rash, and/or internal organ involvement (3). This clinical spectrum extends from minor skin rashes to severe, potentially fatal reactions such as Stevens-Johnson syndrome, toxic epidermal necrolysis, and fumigant liver failure. The incidence of hypersensitivity to fluoroquinolones is rare (less than 1 in 50,000) (4). It is generally accepted that the adverse effects as well as efficacy is related to the molecular structure of the drug.

There are several diagnostic procedures for hypersensitive reactions. Skin prick test is useful to detect immediate-type hypersensitivity, while intradermal tests may be used for immediate-type sensitivity (20 minutes after the test) as well as delayed-type hypersensitivity reaction (after 24-72 hours after the test). However, the purity of the reagents, reagent concentration, and dilution solution of the testing agents may cause tremendous variations in interpretation of test results. Other tests, such as serum quinolone specific IgE detection and lymphocyte transformation tests are not widely available in clinical practice (5).

The factors that predispose individuals to hypersensitivity reactions to a drug are unknown in most cases. Genetic factors have long been postulated to be important, and are being uncovered as the basis of drug-induced hypersensitivity. A prevailing hypothesis in the past was that predisposition to drug response (be its efficacy or toxicity), was determined by a single gene. However, it is now clear that in most cases, drug responses (including drug hypersensitivity) are a multifactorial and multigenic process, with a complex interaction between multiple genes and the environment (6). Each gene may contribute to the risk of developing the hypersensitivity reaction, but each individual gene is neither necessary nor sufficient by itself to cause the reaction.

Levofloxacin is an active L-isomer of ofloxacin that is safe and well tolerated. The overall incidence of possible or probable drug-related adverse effects is 2%-9.9% (7). Compared with some other fluoroquinolones, levofloxacin has a lower incidence of dizziness and phototoxicity. In the first case, the patient developed generalized petechiae 3 days after commencing ciprofloxacin intravenously and 2 days following oral levofloxacin for diverticulitis. This subsequently progressed rapidly to diffuse alveolar hemorrhage (DAH) and respiratory failure confirmed by hemosiderin cells in BAL fluid. The lack of response to diuresis and a normal pulmonary artery occlusion pressure excluded congestive heart failure as a likely cause of hypoxemia. Additionally the dramatic clinical and radiologic response to glucocorticoid therapy with a follow up HRCT of chest one month later revealing improving alveolitis and interstitial thickening strongly suggests a diagnosis of hypersensitive pneumonitis and vasculitis. A review of the literature reveals a case report of levofloxacin induced granulomatous interstitial nephritis (8). The presentation of hypersensitive vasculitis and DAH in our patient is most
likely secondary to a hypersensitive reaction to fluoroquinolones considering the temporal relationship between the exposure to the drug and onset of symptoms.

Ciprofloxacin, a second-generation fluoroquinolone has been marketed worldwide for over a decade with a remarkable safety record. The overall incidence of adverse effects involving the GI tract, CNS and skin is about 6%. Occasional episodes of severe CNS and hepatotoxicity have been reported manifesting as convulsions and serious elevations of liver function tests and liver failure, respectively (4). In the second case, the patient has no history of allergy or sick contacts and subsequently developed high-grade fever, maculopapular skin rash and generalized lymph adenopathy with lymphocytosis following empirical treatment with ciprofloxacin for presumed acute bronchitis. Negative blood culture and BAL culture made infectious cause less likely and the spontaneous resolution of lymph adenopathy and lymphocytosis following discontinuation of ciprofloxacin excluded malignancy. Transbronchial biopsy revealed nonspecific interstitial thickening without granuloma or malignancy, in a distribution similar to the pathology of hypersensitive pneumonitis. A HRCT of the chest 2 weeks later revealed significant resolution of interstitial lung disease consistent with a hypersensitive reaction rather than chronic interstitial lung disease. There has been several cases report of hypersensitive vasculitis due to Ciprofloxacin resulting in acute interstitial pneumonitis by Steiger D et al in 2004 (11). The clinical presentation of this patient is consistent with hypersensitivity vasculitis secondary to ciprofloxacin.

**CONCLUSION**

In conclusion, fluoroquinolones are valuable antibiotics with an overall low risk of adverse effects. However, immunologically mediated hypersensitivity reactions while rare may be severe and even fatal as demonstrated by our two cases. The increased use of newer fluoroquinolones due to their broad antimicrobial spectrum and good oral bioavailability substantially increases the likelihood of the occurrence of hypersensitivity reactions. Improving diagnostic tools, using more specific skin tests, specific IgE detection and cellular tests, is mandatory. There is increasing evidence that drug hypersensitivity reactions are genetically determined. As our knowledge of the human genome improves, this will enable us to develop preventive strategies, and improve drug design to minimize hypersensitive reactions in the future.

**References**

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