Histamine H₁ antagonist levocetirizine as a potential cause of lung injury

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Abstract
Histamine H₁ antagonists rarely cause drug-induced lung injury (DLI). A woman in her 60s, who had been taking antihistaminic levocetirizine for 2 months, presented with progressive cough and shortness of breath. A chest radiograph showed patchy infiltrations on both lower lung fields. Chest computed tomography findings were consistent with non-specific interstitial pneumonia. Serum markers associated with interstitial pneumonias were elevated. Room air arterial blood gas analysis revealed hypoxemia. Restrictive ventilatory impairment was noted with reduced diffusing capacity. Transbronchial lung biopsy specimens demonstrated unclassifiable alveolitis. Steroid pulse therapy was introduced for respiratory distress, but the initial response to treatment was poor. A drug lymphocyte stimulation test was positive for levocetirizine. The interstitial pneumonia improved following withdrawal of levocetirizine. Her illness has not recurred under steroid therapy and the discontinuation of levocetirizine. Antihistaminics may have a potential risk of DLI.

Introduction
Drug-induced lung injury (DLI) is defined as a lung injury that results from the specific use of a drug [1]. The list of causative drugs is expanding, but histamine H₁ antagonists have not been recognized as a common cause of DLI. We report the first case of levocetirizine-induced lung injury.

Case Report
A nonsmoking woman in her 60s presented with a nonproductive cough and shortness of breath. She was otherwise healthy except for seasonal allergic rhinorrhea. She had no history of dust inhalation. Three months prior, she had started taking a 5-mg tablet of levocetirizine hydrochloride, a histamine H₁ antagonist (Xyzal®, GlaxoSmithKline K.K., Tokyo, Japan) daily. She had not been taking any other medications including over-the-counter drugs, Chinese herbs, or supplements. Two months later, she had experienced coughing and progressive dyspnea. She was admitted for further evaluation.

On admission, she had low-grade fever and sinus tachycardia. She had no clubbing or skin rash. Chest auscultation revealed bibasilar fine crackles. A chest radiograph showed patchy infiltrations on both lower lung fields (Fig. 1A). High-resolution computed tomography (CT) scans revealed ground-glass opacities surrounding the bronchovascular bundles and subpleural consolidations with reticular opacities (Fig. 2A).

White blood cell count was 11,680/mm³, with 75% neutrophils and 2% eosinophils. Routine blood chemistry test results were almost normal, except a lactate dehydrogenase of 298 IU/L (normal <150 IU/L). Urinalysis and renal functions were normal. The serum level of C-reactive protein was 1.33 mg/dL (normal <0.03 mg/dL). Anti-nuclear antibodies were undetectable. Levels of rheumatoid factor, immunoglobulin-E, and β-D-glucan were normal. The serum concentrations of Krebs von der
Lungen-6 and surfactant protein-D, both of which are biomarkers specific for interstitial pneumonia, rose to 2929 U/mL (normal <500 U/mL) and 255 ng/mL (normal <110 ng/mL), respectively. Restrictive ventilatory impairment was noted with reduced carbon monoxide diffusing capacity. Room air arterial blood gas analysis revealed oxygen tension of 62 mmHg, carbon dioxide tension of 36 mmHg, and pH of 7.44.

Figure 1. Chest radiographies. (A) On admission, patchy infiltrations were seen in both lung fields. (B) On the sixth day, the response to high-dose steroids was poor. (C) Six weeks after discontinuation of levocetirizine. (D) Five months after discontinuation, the infiltrations were reduced with increasing lung volume.

Figure 2. High-resolution computed tomography scans. (A) On admission, showing ground-glass opacities, consolidations, and reticular opacities. (B) Five months after the discontinuation of levocetirizine. Sub-pleural consolidations have disappeared.
Bronchoalveolar lavage (BAL) fluid did not have a bloody appearance. Cells recovered from the BAL fluid comprised 79% alveolar macrophages, 10% lymphocytes, 6% eosinophils, and 5% neutrophils. Hemosiderin-laden macrophages were absent. No microorganisms including fungi were identified in the BAL fluid. Transbronchial lung biopsy specimens demonstrated unclassifiable alveolitis, without evidence of granuloma formation or eosinophil infiltration (Fig. 3).

The initial diagnosis was idiopathic non-specific interstitial pneumonia with respiratory distress. Intravenous steroid pulse therapy was introduced with 1000 mg/day of methylprednisolone for three days, followed by 60 mg of prednisolone daily. However, the initial response to treatment was considered poor based on the radiograms (Fig. 1B). On the sixth day, levocetirizine was switched to fexofenadine hydrochloride (Allegra®, Sanofi K.K., Tokyo, Japan). Afterwards, the interstitial pneumonia improved gradually. The daily dose of prednisolone was tapered by 10 mg/week.

The clinical course raised the possibility that the drug withdrawal had led to the improvement. A drug lymphocyte stimulation test (DLST) was positive for levocetirizine, with an increase in the [3H]-thymidine uptake by 208% (normal <180%). Six weeks after the cessation of levocetirizine, she was discharged with a prescription for 20 mg of prednisolone daily. The infiltrations were reduced with increasing lung volume (Fig. 1C and 1D). Serial assessment of the chest CT revealed significant disappearance of the consolidations (Fig. 2B). Although a provocaton test was not performed, levocetirizine appeared to be the causative agent of DLI.

**Discussion**

Adverse reactions to H1-antihistaminics commonly stem from their binding to several receptors. Cell-mediated reactions such as fixed drug eruption are rare [2]. H1-antihistaminics have scarcely been associated with DLI, except a single case report of acute eosinophilic pneumonia induced by homochlorcyclizine [3]. In that case, an additive to the tablets was identified as the causative substance [3]. However, this was not true for the present case. Levocetirizine tablets contain cellulose compounds, silicon dioxide, magnesium stearate, titanium oxide, and Macrogol 400 as chemical additions. All of these chemicals are identical to the additives contained in fexofenadine tablets. Considering that fexofenadine did not cause further deterioration, the additives were not considered responsible for the development of DLI.

Deciding whether a clinical event is an adverse drug reaction is often based on clinical judgment. However, the use of semiquantitative diagnostic algorithms reduces disagreement between raters [4]. When scored using the Naranjo algorithm, the probability of a reaction to levocetirizine was rated as “Probable” [4]. The diagnosis of DLI was made according to the latest criteria [1]. First, the patient had a history of exposure to levocetirizine, which can cause adverse drug reactions [2]. Second, the clinical manifestations were in line with DLI. Third, all other causes of interstitial pneumonias were eliminated. Fourth, the interstitial pneumonia improved following drug discontinuation. Our case was not subjected to the most definitive criterion for DLI (i.e. a re-challenge test), and thus, uncertainty remains over whether levocetirizine was unquestionably responsible for DLI.

Exposure to a drug can induce DLI with some latency, ranging from a few weeks to months [1]. Levocetirizine was assumed to cause DLI within two months. Late-onset drug reactions may occur, in part, through T cell-mediated immunity [1]. The DLST detected the sensitization of her peripheral lymphocytes to levocetirizine. However, a positive result does not always mean definitive causality for DLI. DLST-positive drugs often prove to be negative on provocation tests and vice versa [5]. Moreover, the sensitivity and specificity of a DLST depend on the type of drug [1, 5]. Considering its variability and low reliability, the DLST played a supplemental role in the diagnostic process [1]. Fexofenadine, another H1 antagonist, was available as a benign alternative for our patient. The likely explanation comes from the difference in chemical structures of the two drugs [2].

We report here a potential risk for antihistaminics to induce DLI. The outcome was relatively good, but the DLI had a progressive nature partially reversible by steroids. Much attention should be paid to cell-mediated reactions to anti-allergic agents.

**Disclosure Statements**

No conflict of interest declared.
Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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