Probable occupational pneumonitis caused by inhalation of crushed clozapine

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Abstract
We present a case of non-specific interstitial pneumonia (NSIP) probably caused by exposure to inhaled clozapine powder. The patient worked in a pharmacy and crushed clozapine tablets over several years. She presented with insidious onset of breathlessness and had mild hypoxia. High-resolution computed tomography demonstrated centrilobular nodules with peribronchial consolidation. Lung biopsy revealed a mixed cellular and fibrotic NSIP. Her symptoms and radiological findings resolved once exposure to clozapine powder ceased. The clear temporal relationship between increased exposure to inhaled clozapine and the development of NSIP, followed by the subsequent resolution on cessation of exposure, strongly suggest an occupational cause. Both the active ingredients and the excipients of powdered medicine may be responsible for causing pneumonitis in chronic exposure.

Key words
Drugs; lung disease; non-specific interstitial pneumonia; occupational exposure; occupational respiratory disease.

Introduction
Drug-induced lung disease is well recognized in patients taking oral or intravenous medication. The clinical features can vary and depend upon the drug in question, the extent and chronicity of exposure, and host factors. Histological, radiological and pathological features are also extremely variable and frequently non-specific. Features characteristic of non-specific interstitial pneumonia (NSIP) have been described following exposure to a broad range of drugs [1]. Diagnosis rests on excluding other causes and establishing the temporal relationship between exposure and lung disease. Treatment involves removal from exposure to the agent. Corticosteroids and immunosuppressive therapy are reserved for severe or refractory cases [1]. We report the first published case of probable occupational NSIP in a pharmacist with chronic inhalation of clozapine dust.

Case report
A 62-year-old woman presented with a 3-month history of breathlessness and no systemic symptoms. Medical history included Raynaud’s phenomenon and hypothyroidism. She kept no pets or birds. She was an ex-smoker of 15 years, with a 20-pack-year history, and worked as a hospital pharmacist. Clinical examination revealed bibasal crackles. There was no clinical evidence of a multisystem disorder.

At the time of presentation, the patient’s chest radiograph (CXR) showed bibasal infiltrates and small bilateral pleural effusions (Figure 1a). Initial investigations included normal urea and electrolyte levels, full blood count, erythrocyte sedimentation rate of 19 mm/h, c-reactive protein level of 2 mg/l, positive anti-nuclear antibody (ANA) titre 1 : 100 and positive anti-neutrophil cytoplasmic antibody (ANCA) titre 1 : 320. Spirometry revealed a forced expiratory volume in 1 s (FEV₁) of 2.48 (93% of predicted), forced vital capacity (FVC) of 2.11 (94% of predicted) and ratio of 85%. PaO₂ was 10.1 kPa on air. High-resolution computed tomography (HRCT) of the thorax showed multifocal, peribronchial consolidation, with additional centrilobular nodularity (Figure 2).

Surgical lung biopsy appearances were consistent with mixed cellular and fibrotic NSIP (Figure 3).

The patient remained absent from work and, during the subsequent 6 months, symptoms resolved and the CXR appearance improved without drug therapy (Figure 1b). ANA remained positive with a 1 : 40 titre; however, the remainder of her autoimmune and vasculitis serology was negative. The patient returned to work, undertaking limited duties.
The patient worked in a pharmacy. Over the preceding 7 years, she had been crushing clozapine, an atypical antipsychotic, with a pestle and mortar to produce a saline suspension of the medication for administration. Over the 18 months preceding presentation, the quantity of crushed tablets required had risen sharply so that she was crushing ~5000 tablets per month, causing clouds of clozapine dust. Crushing occurred in a small room with no ventilation. She occasionally wore a simple paper face mask and reported being able to taste the powdered drug. By the time she returned to work, the practice of crushing clozapine tablets had been stopped and pre-prepared solutions were being purchased.

The temporal relationship between the onset of symptoms, exposure and subsequent resolution is suggestive of pneumonitis caused by exposure to inhaled clozapine powder.

**Discussion**

The principal differential diagnosis is occupational NSIP and connective tissue disease-associated NSIP. Distinguishing between these two conditions can be difficult. NSIP is the commonest form of interstitial lung disease associated with connective tissue diseases but may also be associated with a diverse range of causes, including a wide variety of drugs. The patient had Raynaud’s phenomenon and temporarily positive ANA and ANCA, raising the possibility of a connective tissue disorder. However, serological abnormalities did not persist and there were no other features to convincingly support a diagnosis of underlying connective tissue disease. The temporal relationship between the onset of symptoms and the increase in exposure to powdered clozapine, followed by the spontaneous resolution of symptoms and
radiological abnormality after removal from exposure, make occupational NSIP the more likely diagnosis.

Drugs can cause a variety of patterns of lung disease, including interstitial lung disease, hypersensitivity reactions, acute respiratory distress syndrome and bronchiolitis obliterans organizing pneumonia [2,3]. Most drug-induced lung diseases are associated with systemic treatment following oral or intravenous administration. A spectrum of hypersensitivity reactions has been associated with the ingestion of oral clozapine, including asthma [4], subacute NSIP [5] and unspecified pulmonary infiltrates. The Medicines and Healthcare Products Regulatory Agency reports 1306 yellow card incidents related to respiratory effects of clozapine taken systematically, including one report of alveolitis, one report of fibrosing alveolitis, one report of pneumonitis, along with various reports of aspiration pneumonia and pulmonary embolus [6]. There have been no reports of pneumonitis caused by occupational inhalation of crushed clozapine.

The particular preparation of clozapine implicated in this case contains several excipients, including magnesium stearate, silica, colloidal anhydrous povidone, talc, maize starch and lactose monohydrate. Talc (magnesium silicate) inhalation can cause acute airway irritation in neonates following overexposure [7]. Subacute or chronic exposure may lead to a form of fibrotic pneumoconiosis termed talcosis [8]. Histological features are characterized by accumulation of free silica in histiocytes [3]. These features were not present in this case.

Cases of infants developing an allergic pneumonitis due to inhaled cornstarch are also described [9]. A pneumonitis could hypothetically be caused by inhaled maize starch through a mechanism similar to that of cornstarch.

In summary, the link between pneumonitis and inhalation of powdered medication has not been described before. A reaction to inhaled powder could theoretically be caused by the active ingredient of a tablet or any of its excipients. In view of our case report, we feel that, although a rare complication, occupational pneumonitis should be borne in mind for the evaluation of any patient exposed to powdered medication who presents with evidence of pneumonitis.

Key points
- Occupational pneumonitis may develop following exposure to inhaled powdered medication.
- Diagnosis of occupational pneumonitis is suggested by a temporal relationship between the development of symptoms with exposure and subsequent improvement following removal from the offending agent.

Conflicts of interest
None declared.

References

Figure 3. Lung biopsy showing architectural distortion, temporally homogenous, diffuse fibrosis and early lymphoid follicle formation.