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Short reports

Tocainide-associated interstitial pneumonitis

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Tocainide (2-amino-2',6'-propionoxy-lidide) is an analogue of lignocaine which is almost 100% absorbed after oral administration. The drug has a plasma half-life of approximately 12 hours and is currently under investigation as an anti-arrhythmic agent for patients with ventricular ectopic beats. It appears that in patients with life-threatening ventricular arrhythmias, tocainide is a safe agent with a favourable risk-benefit ratio.[1] The adverse experiences that have been reported include neurological and gastrointestinal complaints.[2] However, recent reports have suggested that tocainide therapy might be associated with interstitial pneumonitis.[2 3] We record here the occurrence of acute alveolitis in a patient two months after starting tocainide therapy.

Case report

A 72-year-old man with a 50 pack-year smoking history presented with high grade ventricular ectopy associated with ischaemic heart disease. His initial therapy with procainamide, disopyramide, and quinidine was unsuccessful and the arrhythmia remained symptomatic. He responded well to tocainide (400 mg every eight hours) given orally. Two months after an initial marked symptomatic improvement, he developed progressive dyspnoea and reduced exercise tolerance. Examination revealed tachypnoea, central cyanosis, basal lung crackles but no clubbing of the fingers. There was no clinical evidence of cardiac failure, but the chest radiograph, which had at the start of tocainide therapy been clear, showed a diffuse infiltrate. Gallium 67 (^{67}Ga) scintigraphy was diffusely positive and pulmonary function testing revealed increased alveolar ventilation, a widened alveolar-arterial oxygen tension gradient, and reduced diffusing capacity and total lung capacity (table). Bronchoalveolar lavage performed at the time of open lung biopsy showed a predominant polymorphonuclear leukocytosis of 21% of lavaged cells, with normal microbiology. Open lung biopsy showed an active alveolitis with chronic diffuse interstitial pneumonitis and early fibrosis. Rheumatoid and anti-nuclear factors were negative and the serum complement level was in the normal range.

Within one week of stopping tocainide and starting prednisone (60 mg/day) the patient noted improvement in his dyspnoea and exercise tolerance. Prednisone therapy was continued for four weeks and then tapered

Table *Pulmonary function tests at the time of diagnosis of diffuse interstitial disease*

Age: 72 years Sex: male Weight: 67 kg		
	l	*% predicted*
FEV_1	2·5	109
Vital capacity	3·0	90
Total lung capacity	5·7	100
Functional residual capacity	4·2	127
DLCO (ml/min. mmHg)	9·8	42
	l/s	
$\dot{V}50$	4·4	133
$\dot{V}25$	1·1	65
	Rest	*Exercise*
Pao_2 (mmHg) on room air	70	52
$Paco_2$ (mmHg) on room air	30	32

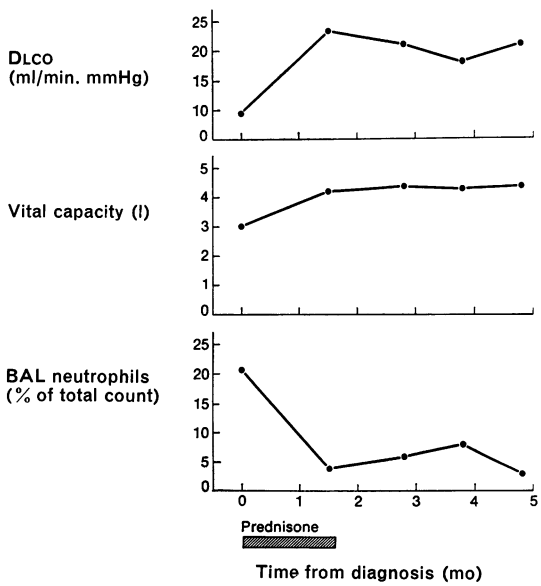

Figure *Time-course of diffusing capacity* (DLCO), *vital capacity, and neutrophil count in bronchoalveolar lavage fluid in relation to prednisone therapy and after cessation of tocainamide.*

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off over 14 days. During this time there was radiological clearing of the lungs, improved pulmonary function and reduction of the polymorphonuclear leucocyte count in the bronchoalveolar lavage fluid. Gallium 67 scintigraphy showed residual patchy uptake for a further eight weeks, but by 12 weeks after prednisone withdrawal, both ^{67}Ga scintigraphy and bronchoalveolar lavage differential cell counts were normal (figure).

Discussion

Some 130 causes of interstitial lung disease have been described, but at least 60% of patients fall into an "idiopathic" group.[4] In our patient, search for a cause, including open lung biopsy, revealed none. However, the temporal relationship of the pneumonitis to tocainide therapy threw suspicion on this agent. Subsequently, two reports of interstitial lung disease developing in three patients on tocainide therapy have appeared.[2 3] In one of these patients transbronchial biopsy confirmed the presence of an interstitial pneumonitis, but in none was the cellular activity of the alveolitis assessed or followed serially.

Ideally, in the diffuse lung disorders, disease activity is evaluated by lung biopsy, ^{67}Ga scintigraphy, and a differential cell count of bronchoalveolar lavage (BAL) fluid, the latter two lend themselves to serial use.[4] In Hutchinson's algorithm for the operational assessment of adverse drug reactions,[5] the questionnaire stresses the importance of "dechallenge", in which clinical manifestations are related to the time-course of drug cessation. Repeated use of the techniques available to assess disease activity in the lung and the previously documented temporal association have allowed two independent numerical scores of likelihood of an adverse drug reaction to tocainide to be made. The resulting numerical score of +4 in the adverse drug reaction algorithm provided a "probable" association between tocainide and interstitial pneumonitis in this patient.

To the best of our knowledge, there have been no previous reports of BAL and ^{67}Ga scintigraphy in drug-induced pulmonary interstitial diseases. These techniques demonstrated that, as in idiopathic pulmonary fibrosis,[4] as opposed to sarcoidosis, the dominant alveolar cellular abnormality is the presence of polymorphonuclear leucocytes. They persisted at a low level of activity for several weeks after the radiographic and physiological features had returned to normal. Despite the absence of a drug re-challenge, we conclude that an adverse reaction to tocainide in the form of diffuse interstitial pneumonitis probably occurred.

References

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