

Fatal lupus-like syndrome and ARDS induced by fluvastatin

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A woman aged 67 years was admitted to hospital with an 8-week history of polyarthralgia, aches and pains in the muscles, and a generalised rash. She was known to have hypertension, which was controlled with atenolol 50 mg daily. She had a history of retinal-vein thrombosis about 2 years before admission, after which she was placed on aspirin 75 mg daily. At a routine screening about 6 months before admission to hospital she was hypercholesterolaemic, with a serum cholesterol of 7.2 mmol/L. Dietary measures were unsuccessful in lowering her cholesterol and she was placed on fluvastatin 20 mg daily. 1 week after she started the drug she noted an itchy, generalised, erythematous rash, followed by swelling and pain in her right knee and joints of both hands. She discontinued fluvastatin after about 10 weeks, but the symptoms had not resolved after more than 1 month after discontinuation of the drug, and she attended hospital.

On admission she looked unwell. Her pulse rate was 92 beats per min; blood pressure 180/100 mm Hg. She was apyrexial. An erythematous maculopapular rash was seen mainly on sun-exposed areas. The facial rash was in a "butterfly" distribution. The small joints of the hands were swollen; there was periungual erythema and telangiectasia. Lung-field assessment showed crackles in both lung bases. Routine serum chemistry showed normal urea and electrolytes, raised concentration of C-reactive protein at 43 mg/L, mild derangement of liver function, and normal creatine kinase concentration. Full blood count was normal. Erythrocyte-sedimentation rate was 31 mm in the 1st h. Initial serum autoantibody screen was negative, as was rheumatoid factor; serum complement concentrations were normal; a subsequent test for double-stranded DNA by ELISA was positive at 274 (normal <50). Tests for antihistone and anticentromere antibodies were negative.

In the first few days after admission the patient became increasingly breathless. Lung-function tests showed a restrictive defect with decreased lung volumes (vital capacity 73% predicted with a normal forced expiratory volume in 1 s/forced vital capacity ratio) and diminished diffusing capacity (39% predicted). Analysis of serial arterial blood gases showed worsening type 1 respiratory failure. Computed tomography of the thorax showed extensive abnormalities of both lung fields, with possible widespread alveolitis and some areas of fibrosis. Bronchoscopy and bronchoalveolar lavage showed no endobronchial abnormality or opportunistic infection. Skin biopsy from an involved area showed a perivascular lymphocytic infiltrate in the dermis and areas of diffuse necrosis within the epidermis with incipient blister formation, features suggestive of subacute lupus, and erythema multiforme. An open lung biopsy revealed diffuse alveolar damage with hyaline membrane, intra-alveolar organisation, and atypical reactive pneumocytes characteristic of drug-induced lung damage, but no evidence of vasculitis or granuloma formation.

Shortly after admission, the patient's symptoms improved with non-steroidal anti-inflammatory drugs; however, the patient's respiratory status deteriorated progressively. High-dose steroids (pulsed intravenous methylprednisolone 1 g daily for 3 days) improved her skin lesions but her respiratory status continued to deteriorate. Despite assisted ventilation, and immunosuppressive therapy with cyclophosphamide, she died. At necropsy, the lungs showed signs of adult respiratory distress syndrome (ARDS). There was evidence of coronary atheroma; a small vegetation of

uncertain relevance was noted on the mitral valve.

In general, statins (HMG Co-A reductase inhibitors) are well tolerated and have been shown to be effective in the primary and secondary prevention of coronary heart disease.^{1,2} There have been previous reports of lupus-like syndrome in patients on statins.^{3,4} In the cases involving lovastatin³ and simvastatin,⁴ the symptoms were mild and resolved when the statin was stopped and small doses of oral steroids started. One patient with systemic lupus erythematosus induced by lovastatin had features of pulmonary involvement with radiological appearances of pneumonitis.³

We could not identify previous reports of fatal lupus-like reaction with pulmonary toxicity resulting in an ARDS-like syndrome. No such effects have been reported to the Committee on Safety of Medicine in the UK or manufacturers of statins (personal communications). Our findings may show a class effect rather than an effect restricted to an individual statin. Since the illness was severe and rapidly led to death, it was not possible to fulfil conventional criteria for diagnosis of a drug-induced reaction. The absence of other causes for the clinical syndrome described, previous reports of a similar (albeit milder) cases, the temporal relation of the symptoms to the drug therapy, and the characteristic toxic appearances on lung biopsy argue in favour of an adverse reaction to fluvastatin. A single fatality from a side-effect should not alter prescribing policy, but should lead to greater vigilance and awareness of the potential side-effects and early withdrawal of treatment should suggestive systems occur.

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RM # 10

Nutrient intakes among UK African-Caribbeans: changing risk of coronary heart disease

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Coronary heart disease (CHD) mortality in the UK for Caribbean-born people, who are mainly of African descent, continues at less than half the national average for men, and two-thirds for women.¹ Nutrient intake is a major contributor to coronary risk but little dietary information is available for the African-Caribbean population in Britain.

We developed a specific food-frequency questionnaire (FFQ) with the local African-Caribbean community to assess food consumption during the previous 12 months. This was part of an international study;² in the UK, a random sample of people aged 25-79 years from four general-practice population registers serving inner-city

| | African-Caribbean men (n=85) | NDNS white men (n=273) | African-Caribbean women (n=125) | NDNS white women (n=283) |
|-----------------------------------|------------------------------|------------------------|---------------------------------|--------------------------|
| Mean age (years) | 57.1 | — | 51.2 | — |
| CI or range | CI 54-60 | Range 50-64 | CI 49-54 | Range 50-64 |
| Mean BMI (kg/m ² ; CI) | 27.0 26.3-27.7 | 25.9 25.5-26.3 | 28.7 27.7-29.8 | 26.2 25.5-26.9 |
| Energy (kcal) | 2334 | 2380 | 1926 | 1610 |
| CI | 2142-2526 | 2319-2441 | 1802-2051 | 1564-1656 |
| (kilojoules) | 9765 | 9958 | 8058 | 6738 |
| CI | 8962-10 569 | 9703-10 213 | 7540-8581 | 6544-6929 |
| % from fat | 32.0 | 37.6 | 32.6 | 39.5 |
| CI | 30.9-33.1 | 37-38.2 | 31.7-33.5 | 38.9-40 |
| % saturated fat | 11.5 | 16.1 | 11.9 | 17.1 |
| CI | 10.3-12.7 | 15.7-16.5 | 10.7-13.0 | 17.3-17.5 |
| % carbohydrate | 48.9 | 41.4 | 51.0 | 42.3 |
| CI | 47.2-50.5 | 40.6-42.2 | 49.9-52.1 | 51.9-42.7 |
| % alcohol | n=77 | | n=103 | |
| (drinkers only) | 3.9 | 8.1 | 1.6 | 3.5 |
| CI | 3.0-4.9 | 7.1-9.1 | 1.3-1.9 | 2.9-4.1 |
| % protein | 14.9 | 14.7 | 14.7 | 16.1 |
| % CI | 14.5-15.3 | 14.4-15.0 | 14.3-15.1 | 15.7-16.5 |

kcal to kilojoules: $\times 4.184$, CI=95% confidence intervals, NDNS=National Diet and Nutritional Survey of British Adults.²

Age, body-mass index (BMI), and total dietary energy intake with percentage of energy from macronutrients for UK African-Caribbeans and a national UK sample

Manchester were invited to take part in a blood pressure and glucose tolerance survey (67% response). The FFQ was completed once, between 1992-1995, by 85 African-Caribbean men and 125 women (83% response), all of whom had at least three grandparents of African ancestry born in the Caribbean. The FFQ included foods contributing at least 90% of total energy, fat, carbohydrate, and protein, as developed from and later compared against three-day food diaries (n=41; diary: questionnaire correlation, Spearman's rank $r=0.55$ for energy, for fat $r=0.5$). Interviewers determined frequency and usual portion size for 108 Caribbean and European foods. Nutrient composition was calculated from local recipe collection and food tables.²

We compared our results with those for people of similar ages in the National Diet and Nutrition Survey's (NDNS) almost entirely white population sample, whose nutritional intake was assessed by the different method of 7-day weighed record² (table). We found that African-Caribbeans consumed less energy from fat, particularly saturated fat, and from alcohol, and hence more from carbohydrate. Older African-Caribbeans aged 65-79 years (n=32) and 55-64 years (n=76) consumed 31.2% and 32.3% of total energy from fat (95% CI 29.1-32.9% and 31.1-33.5% respectively). However, in those aged 25-34 years (n=43) fat intake was 34.9% (33.5-36.3%); test for trend by age, $p<0.01$, reflecting less traditional Caribbean and more European foods such as cakes and biscuits. In NDNS, mean proportional energy from fat was 37.6 (37.3-37.9)% in men and 39.2 (38.9-39.5)% in women, which was similar across each age decade (n=189-385) from 16-64 years (3, p91).

This average African-Caribbean diet already falls within national recommendations for fat intake as less than 35% of food energy (32.5% here) and less than 15% as saturated fat (11.8% here). Fruit and green vegetable intakes were also higher in African-Caribbeans here (data not shown). Although association alone cannot support causal relations, our findings are compatible with the lower CHD standardised mortality ratios of Caribbeans in the UK.¹ NDNS used different dietary assessment methodology so comparison has to be cautious; however fat intakes and CHD rates have generally been higher in poorer inner-city populations increasing the contrast with results here. Our

results are consistent with the only previous small studies in representative African-Caribbean samples (11 men and 23 women) using weighed-records which found percent energy from fat of 32.6% and 35.8% respectively.^{4,5} The high mean body-mass index in African-Caribbeans, particularly women, suggests that while the quality of the diet is as recommended, quantities consumed are too great for the level of energy expenditure. Increasing percentage energy from fat in the younger compared with older African-Caribbean age group suggests that coronary risk profiles are changing, as other migrant communities have experienced. Notably, in Jamaica, the origin of over 60% of our African-Caribbean population, CHD mortality in 1990 was half that of Caribbean-born people in the UK.

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ACE inhibitors and symptomless dysphagia

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Elderly patients with symptomless dysphagia have decreased cough reflexes.¹ Angiotensin-converting enzyme (ACE) inhibitors induce coughing. We investigated whether a correlation exists between patients with symptomless dysphagia with either cerebral infarction or cerebral haemorrhage and elimination of low serum substance P concentration by ACE inhibitors.²

16 patients (seven men and nine women) with histories of cerebral infarction or cerebral haemorrhage, all with hypertension and symptomless dysphagia, were classified as group A.

Ten outpatients (six men and four women) on an ACE-inhibitor (imidapril hydrochloride³) for hypertension, all with no dysphagia, were selected as group B. We also included seven healthy controls. We obtained informed consent from patients or their families.

In patients with cerebral infarction or cerebral haemorrhage, symptomless dysphagia increases at night because the cough reflex is weakened during sleep.¹ To find the occurrence of symptomless dysphagia, we gave 1 mL Technetium Tin Colloid (^{99m}Tc) to patients in group A during sleep via a nasal catheter.⁴ At 0900 h the next day we checked for symptomless dysphagia by imaging. We had given all patients 5-10 mg daily imidapril hydrochloride orally. We measured serum substance P, bradykinin, and prostaglandin before and 12 weeks after administration. Simultaneous administration of other medications was allowed except for L-dopa.⁵

Mean serum substance P was low in group A (group A 23.3 pg/mL, group B 76.5 pg/mL, controls 72.7 pg/mL).