SIDE EFFECTS OF DRUGS

Levamisole-induced arthritis in Crohn's disease

In Crohn's disease neutrophils accumulate abnormally slowly at a site of acute inflammation,[1] a defect which may be related to the pathogenesis of the disease. Levamisole is thought to stimulate defective immunity non-specifically, and, in particular, to stimulate neutrophil migration.[2] We performed a study to determine whether levamisole could maintain patients with Crohn's disease in remission after this had been induced by treatment with an elemental diet. Two of the eight patients managed in this way developed a severe arthritis which was closely associated with levamisole administration and subsided after withdrawal of the drug.

Case 1

A 22-year-old man developed diarrhoea, colicky abdominal pain, and weight loss in May 1976. He had noticed occasional aching in his left elbow and knee. There was no swelling or limitation of movements in these joints and no radiological abnormality. He was feverish and his spleen was enlarged 2 cm below the costal margin. Barium studies showed mucosal ulceration of the terminal ileum and caecum and stenosis of the affected ileum. An infective cause for these lesions was not found and Crohn's disease was diagnosed, the only atypical feature being selective IgA deficiency (IgA 0·13 g/l, IgG 15·1 g/l, IgM 1·4 g/l). He was given an elemental diet for a month, and after the first two weeks he received levamisole 150 mg/day for three consecutive days every two weeks. Clinical remission was induced within a few days of starting the elemental diet.

Five months after starting levamisole treatment side effects were observed. Twelve hours after the first dose in each fortnight his left knee and elbow became painful and swollen with effusions. He also became feverish and developed mild proteinuria (1·2 g/day). These abnormalities resolved spontaneously the day after the final dose of the drug. This sequence of events was exactly repeated with the next three-day course of levamisole. On this occasion a sample of synovium taken from the left knee by needle biopsy showed mild non-specific inflammation with a few small deposits of immunoglobulins and C3. Synovial fluid did not show evidence of complement consumption, formation of complement split products (rabbit antihuman B_1C/B_1A—globulin serum; Behringwerke),[3] or immune complexes,[4] and the cell count was 15×10^9/l (90% neutrophils, 10% mononuclear cells). The comparison of serum samples taken before and during treatment showed no major changes in complement concentrations or immune complex generation. Transformation[5] by lymphocytes from the patient and normal subjects exposed to levamisole (0·01, 0·1, 1·0 mg/l) in autologous, pooled normal, or fetal calf serum (10%) did not differ from the baseline control values, although transformation was normal in response to phytohaemagglutinin. Precipitating antibodies in the serum were not observed by immunodiffusion. Levamisole treatment was stopped and there was no further evidence of joint disease.

Case 2

A 30-year-old woman developed severe watery diarrhoea, weight loss, and fever in August 1975. Crohn's disease was diagnosed on the basis of the barium enema examination, which showed extensive ulceration of the colon from the caecum to the sigmoid colon, and rectal biopsy, which showed a histiocytic granuloma. She initially responded to bowel sterilisation[6] but later relapsed and was treated with the same regimen as the first patient. Before starting levamisole treatment she had occasional stiffness in the hands and back, but there was no swelling of the joints and no radiological abnormality.

Three months after starting levamisole she developed generalised arthritis on three successive courses of treatment. In each case the arthritis had an identical pattern but it increased in severity with each course. Twelve hours after the first dose she noticed the gradual onset of generalised pain in the joints. This was particularly severe in her hands, which became swollen; cervical spine; and temporomandibular joints. On the third occasion these symptoms were so severe that she could not eat, grasp objects, or walk. Symptoms resolved spontaneously 24-48 hours after stopping the drug and did not recur after withdrawal of treatment. There were no residual symptoms or signs of joint damage. Three months after stopping treatment precipitating antibodies to the drug were not shown in serum, and blast transformation of lymphocytes did not occur.

Comment

Two of the eight patients with Crohn's disease whom we have treated with levamisole developed severe arthritis. Both these patients had had mild arthralgia, with a distribution similar to that of the arthritis associated with drug administration. The absence of reports of levamisole-induced arthritis, despite the drug's wide use for various conditions, including malignant and rheumatic diseases, sarcoidosis, and viral skin disease,[7] suggests that this complication is specifically related to Crohn's disease. There was no evidence that immune complex formation or complement activation were concerned, and precipitating antibodies to or lymphocyte activation by levamisole were not detected with the methods used. It seems likely that the drug induced an arthritis, an accepted complication of Crohn's disease,[8] in these patients by unmasking latent mechanisms of joint damage.

Elucidation of the mechanisms of action of levamisole should give valuable insight into the pathogenesis of the arthritis associated with Crohn's disease and possibly arthritis in general.

We thank Dr J Winfield for performing the synovial biopsy on the first patient.

1 Segal, A W, and Loewi, G, *Lancet*, 1976, **2**, 219.
2 Anderson, R, *et al*, *Journal of Immunology*, 1976, **117**, 428.
3 Laurell, C B, *Analytical Biochemistry*, 1965, **10**, 358.
4 Zubler, R H, and Lambert, P H, *Annals of the Rheumatic Diseases*, 1977, **36**, suppl No 1, p 27.
5 Lance, E M, and Knight, S C, *Arthritis and Rheumatism*, 1974, **17**, 513.
6 Kane, S P, *Proceedings of the Royal Society of Medicine*, 1976, **69**, 266.
7 Rosenthal, M, Trabert, U, and Muller, W, *Scandinavian Journal of Rheumatology*, 1976, **5**, 216.
8 Ansell, B M, and Wigley, R A D, *Annals of the Rheumatic Diseases*, 1964, **23**, 64.

(*Accepted 30 May 1977*)

Clinical Research Centre, Harrow, Middlesex
A W SEGAL, MD, MRCP, clinical scientist
S F PUGH, MB, MRCP, research fellow
A J LEVI, MD, FRCP, consultant gastroenterologist
G LOEWI, DM, FRCPATH, consultant pathologist

Levamisole-induced thrombocytopenia

Levamisole (L-tetramisole) is an anthelmintic drug with immunostimulating capacity in certain immunodeficiency states,[1] which has been reported to have beneficial effects in rheumatoid arthritis.[2] We are currently assessing the drug in adults with rheumatoid arthritis, and we report here a patient with rheumatoid arthritis who developed thrombocytopenia while taking levamisole.

Case report

A 59-year-old woman was first seen at the outpatient department on 7 October 1976 with a six-month history of polyarthritis. The Ritchie articular index of joint tenderness[3] was +19. There were no subcutaneous nodules and no hepatosplenomegaly. The rheumatoid factor test (R3 test) was strongly positive at a titre of 1/512 and the antinuclear factor titre was 1/16 (homogenous pattern). Joint radiographs showed erosive changes in the hands and feet. Other laboratory investigations showed: haemoglobin 11·2 g/dl, total white cell count $8·2 \times 10^9$/l, platelets 177×10^9/l, and erythrocyte sedimentation rate 44 mm in the first hour. Other biochemical values were normal. A chest radiograph showed nothing abnormal.

The patient was treated with indomethacin 200 mg/day and oral iron. Despite the large dose of indomethacin she continued to suffer severe joint pain, and feprazone (pyrazolidinedione derivative; Meprazone; Boehringer Ingelheim Ltd) 600 mg/day was started on 25 November. Because she failed to respond to feprazone, the patient was started on levamisole on 7 January 1977 in a daily dose of 150 mg. Naproxen 750 mg/day was also begun and feprazone discontinued. On 11 February the platelet count was reduced at