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 B₂C/B₂A—globulin serum; Behringwerke),³ or immune complexes,⁴ and the cell count was $15 \times 10^9/l$ (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. Transformation⁵ 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 sterilisation⁶ 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.

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⁶ Kane, S P, *Proceedings of the Royal Society of Medicine*, 1976, 69, 266.

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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 tenderness³ 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 $177 \times 10^9/l$, 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

$31 \times 10^9/l$. Levamisole was immediately discontinued and a week later the platelet count had returned to normal ($150 \times 10^9/l$). Levamisole was restarted in a dose of 100 mg/day. On 21 March 1977 the platelet count had again fallen to $87 \times 10^9/l$. The haemoglobin concentration was 13.3 g/dl and the total white cell count $5.7 \times 10^9/l$. Levamisole was discontinued and on 14 April 1977 the platelet count was again normal ($159 \times 10^9/l$).

Comment

Although agranulocytosis has been reported in patients with rheumatoid arthritis taking levamisole,⁴ we can find no report of thrombocytopenia caused by levamisole therapy. Our patient was receiving only naproxen and levamisole when thrombocytopenia developed. The platelet count quickly returned to normal on stopping levamisole despite the fact that naproxen was continued. When levamisole was reintroduced in a smaller dose thrombocytopenia again resulted, and the platelet count again quickly returned to normal on stopping the drug. Levamisole was therefore almost certainly the agent responsible for the thrombocytopenia. We did not consider it justified to carry out bone marrow examination, especially as the patient was rather nervous at the thought of the procedure.

Patients with rheumatoid arthritis inevitably suffer from polypharmacy. This patient had previously taken indomethacin in a relatively high dose of 200 mg and had also received feprazone.

Indomethacin has only rarely been reported as a possible cause of thrombocytopenia.⁵ Feprazone has a pyrazolidine ring in common with phenylbutazone and as such might have the potential for causing thrombocytopenia. But no case of thrombocytopenia has so far been reported with feprazone treatment. It thus appears that levamisole was the likely cause of a low platelet count in this patient.

¹ *Lancet*, 1975, 1, 151.

² Huskisson, E C, *et al*, *Lancet*, 1976, 1, 393.

³ Ritchie, D M, *et al*, *Quarterly Journal of Medicine*, 1968, 37, 393.

⁴ Ruuskanen, O, *et al*, *Lancet*, 1976, 2, 958.

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SHORT REPORTS

Return to work after aortofemoral bypass surgery

The effect of aortofemoral bypass surgery on the return to full employment of 51 members of the working population is described.

Methods and results

All patients aged 60 or under who had undergone aortofemoral bypass for severe intermittent claudication or rest pain during 1973-5 at the Royal Victoria Infirmary, Newcastle upon Tyne, or at the Newcastle General Hospital, were sent the following questionnaire:

- What was your job before you had problems with the arteries in your legs?
- Before the operation were you forced to stop work because of the arteries?
- After a period of convalescence did you get back to work? If yes, how long after operation?
- If you did return to work did you have to change your type of work?
- If you did not return to work, was this because you were unable to manage your previous job?
Or were you made redundant?
Or could you not return because of some other medical illness. If yes, please specify.
- If you were unemployed before the operation did you find employment after operation?
If you did find employment after operation was this as a result of the improvement produced by the operation?

There were 53 patients aged 44 to 60, eight of them women. All the patients had been in regular employment. One patient had died from a myocardial infarction shortly after return home and one could not be traced. The progress of the remaining 51 patients is summarised in the figure.

Of the 35 patients who returned to work, the average interval between operation and return to work was 4-5 months. Sixteen patients did not return to work after operation. Of the thirteen who had not worked before operation, ten were men. Of these, four had either myocardial or cerebrovascular problems, one had unrelated malignant disease, two became redundant, and the remainder felt they "just could not manage." Of the three women who did not return, one had developed an upper limb occlusion and the others had been advised to retire by either medical board or spouse, although all three commented on a definite postoperative improvement at the end of the questionnaire, and none complained of difficulties in performing routine housework. Of the remaining three patients who had worked before operation, the first sustained a myocardial infarction, the second a myocardial infarction with a cerebrovascular accident later, and the third was offered early retirement.

Working history in relation to aortofemoral bypass.

Comment

When judging the success of vascular operations patency rates tend to be quoted and the patient's return to a normal working life forgotten. In this series 29 patients were totally lost to productive employment before operation. Sixteen of these returned to active employment, 14 to their original work, and this was in a region of high unemployment. The current economic climate must naturally invite medical audit and cost-effectiveness studies.^{1 2} Without taking into account any other benefit produced by aortofemoral bypass, we conclude that the operation produces a definite return to employment in those who would otherwise draw permanent sickness benefit.

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¹ *British Medical Journal*, 1975, 4, 723.

² *Lancet*, 1976, 1, 132.

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