polyradiculoneuropathy of subacute onset, seems to be more in keeping with an immunologically induced demyelination.

I thank Dr E C Hutchinson, North Staffordshire Royal Infirmary, for his permission to report this case.


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Regional Department of Neurology, Derbyshire Royal Infirmary, Derby DE1 2QY
R N CORSTON, MB, MRCP, senior registrar

Pregnancy attributable to interaction between tetracycline and oral contraceptives

Various drugs, including antibiotics, may cause failure of contraception and breakthrough bleeding in patients on oral contraceptives. Early reports implicated rifampicin, which was later shown to increase the rate of hepatic metabolism of ethinyl oestradiol and norethisterone. There have been three cases of pregnancy in women taking ampicillin. We cannot find any report of either breakthrough bleeding or pregnancy attributable to tetracycline in a woman taking oral contraceptives. We report such a case.

Case history
The patient, a 20-year-old student, had been taking oral contraceptives for four years. Her only complaint had been of an increase in left-sided headaches. For the last two years she had taken Microgynon 30 (ethinyl oestradiol 30 μg, β-norgestrel 150 μg) and had had no breakthrough bleeding. On 16 October 1978 she had a normal withdrawal bleed. On 20 October she started the next course of Microgynon and also (for sinuses) a five-day course of tetracycline 500 mg six hourly for three days and 250 mg six hourly for two days. She completed the course on the 24 October. She did not forget to take her oral contraceptive. She had no diarrhoea or vomiting but had only a very light two-day withdrawal bleed on 14 and 15 November 1978. She continued to take her oral contraceptive for a further two months until she was interviewed at the contraceptive clinic on 8 January 1979. Her uterus was then of the size of at least a 12-week pregnancy. This would have corresponded with a previous menstrual period on about the 15 October, and indicated that she must have ovulated either when she was taking the tetracycline or in the week after. Termination confirmed the clinical assessment of the duration of pregnancy.

Comment
The time course of this history in a woman who had been taking oral contraceptives for four years with no problems strongly suggests that the tetracycline contributed to the failure in contraception. In addition to the reports of pregnancies associated with rifampicin and ampicillin, pregnancies have been reported in women taking either sulphamethoxydiazine or chloramphenicol and also an increased incidence of breakthrough bleeding in women on phenoxymethylpenicillin, neomycin, or nitrofurantoin. The mechanism of the interaction is unknown but a decrease in urinary oestriol output has been noted in pregnant women taking ampicillin, phenoxymethylpenicillin, or neomycin. Therefore the enterohepatic circulation of contraceptive steroids may be interrupted by inhibition of the gut bacteria normally responsible for hydrolysis of steroid conjugates. This would result in lower-than-normal concentrations of circulating steroids. There seems no reason why tetracycline should not cause a similar change.

With the widespread use of low-dose oestrogen contraceptives such interactions may well occur more often. Tetracyclines are used for a wide range of infections including pelvic inflammatory disease and non-specific urethritis. One of us has seen a second case of breakthrough bleeding associated with a course of tetracycline. We therefore think that doctors should be aware of the potential problem. We would advise that women taking low-dose oral contraceptives should take extra precautions against conceiving in any cycle during which antibiotics are given.


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Family Planning Association of Western Australia, 233 Adelaide Terrace, Perth, Western Australia
JANET F BACON, MB, medical officer
University of Western Australia, Nedlands, Western Australia 6009
GILLIAN M SHENFIELD, DM, MRCP, senior lecturer in clinical pharmacology

Diet and ulcerative colitis

The apparent rarity of ulcerative colitis in developing countries together with the ability of dietary fibre to affect colonic function and bacterial metabolism have led to suspicions that a low intake of fibre may be a causal factor in this disease. People who develop Crohn’s disease (a closely related condition) show significant differences in diet from matched controls, eating less raw fruit and vegetable fibre and more refined sugar. To investigate whether ulcerative colitis is preceded by an unusual diet we have compared the diet before illness of patients with newly diagnosed colitis with that of closely matched, healthy subjects.

Subjects, methods, and results
Thirty consecutive newly diagnosed patients (17 men, 13 women) were studied. The diagnosis of ulcerative colitis was based on the findings of barium radiology, sigmoidoscopy, and rectal biopsy. In 10 patients the disease extended proximal to the splenic flexure, in five it was limited to the rectum, and in the remaining 15 it was of intermediate extent. The median duration of symptoms before diagnosis was two months (range 1-18). All patients were interviewed within three months of diagnosis. A single dietitian used the dietary history method to question each patient about his or her habitual diet before illness. Using a specially designed questionnaire, she determined the frequency of consumption and size of helpings of each of a comprehensive range of foods and drinks. The data were analysed to determine the average daily intake of different food components with the use of a computer programme compiled from McCance and Widdowson’s food tables. Dietary intake of 30 patients with ulcerative colitis before their illness and that of 30 matched, healthy controls. Results given in g/day as means ± SE of mean unless stated otherwise

<table>
<thead>
<tr>
<th>Patients</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total dietary fibre</td>
<td>199 ± 11</td>
</tr>
<tr>
<td>Cereal fibre*</td>
<td>86</td>
</tr>
<tr>
<td>Total fruit and vegetable fibre</td>
<td>10 ± 0.6</td>
</tr>
<tr>
<td>Raw fruit and vegetable fibre</td>
<td>14.2 ± 0.2</td>
</tr>
<tr>
<td>Refined sugar</td>
<td>96 ± 9</td>
</tr>
<tr>
<td>Total carbohydrate</td>
<td>291.2 ± 20</td>
</tr>
<tr>
<td>Protein</td>
<td>78.4</td>
</tr>
<tr>
<td>Fat</td>
<td>101.6</td>
</tr>
<tr>
<td>Energy (MJ/day)</td>
<td>10.2 ± 0.6</td>
</tr>
</tbody>
</table>

*Median value.
Conversion: SI to traditional units—Energy: 4.2 MJ = 1000 kcal.

With the widespread use of low-dose oestrogen contraceptives such interactions may well occur more often. Tetracyclines are used for a wide range of infections including pelvic inflammatory disease and non-specific urethritis. One of us has seen a second case of breakthrough bleeding associated with a course of tetracycline. We therefore think that doctors should be aware of the potential problem. We would advise that women taking low-dose oral contraceptives should take extra precautions against conceiving in any cycle during which antibiotics are given.


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The control subjects had recently attended the fracture clinic and were otherwise healthy. They were matched with the patients for age (±5 years), sex, social class, and marital status and were not significantly different from the patients in height or weight distribution. The controls were interviewed about their diet in the same manner as the patients. The statistical significance of differences was calculated by Student's t test or by Wilcoxon’s rank sum test for paired data.

The table shows the dietary intake of the patients and controls. There was no significant difference in any food component between the two groups. In particular, there was no difference in the intake of dietary fibre or refined sugar.

Comment

There is apparently no difference between the diet before illness of patients with ulcerative colitis and that of closely matched controls. This contrasts with our findings in patients with Crohn’s disease and suggests that, despite their similarities, these two diseases do not have an identical aetiology. Our data rule out the possibility that individuals develop ulcerative colitis because their intake of fibre is lower than the British average. Nevertheless, the average diet in this country differs in many respects from that of communities in which colitis is apparently rare. Hence, it remains possible that the average British diet favours the development of ulcerative colitis in susceptible individuals.


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University Department of Medicine, Bristol Royal Infirmary, Bristol BS2 8HW
J R THORNTON, MB, MRCP, research fellow
P M EMMETT, BSc, SRD, senior dietitian
K W HEATON, MD, FRCP, reader in medicine

Cimetidine and thrombocytopenia

Since the introduction of cimetidine there have been sporadic reports of associated blood dyscrasia. Uncomplicated thrombocytopenia has been recorded in only three patients,1 2 in whom factors other than cimetidine treatment may have been implicated. I report a case in which the relation of treatment with cimetidine to the development of thrombocytopenia is apparently clear cut and which may elucidate the mechanism by which thrombocytopenia is induced.

Case report

A 43-year-old Tanzanian Asian man with sarcoidosis manifesting as arthritis and lymphadenopathy (treated only with indomethacin) was admitted with polyserositis, polylymphadenitis, and polyarthritis. He had developed hepatomegaly and had anaemia and hypercalcaemia (plasma calcium concentration 3.2 mmol/l, 12.8 mg/100 ml). His platelet count was 184 x 10^9/l (184,000/μl). A small, lesser-curve gastric ulcer was detected radiologically and endoscopically.

Indomethacin was stopped, and he was given cimetidine 1 g daily and prednisolone 20 mg daily, with resolution of his arthritis, lymphadenopathy, and hypercalcaemia. Forty-nine days after beginning cimetidine, while taking prednisolone 10 mg daily, he was readmitted with a two-day history of sore throat and oral ulceration and bleeding. Examination disclosed haemorrhagic blisters on the tongue and buccal mucosa and petechiae in the pharynx, round the mouth, and on the lower legs. There was no lymphadenopathy, and his spleen was barely palpable. His platelet count was 6 x 10^9/l (6000/μl), haemoglobin concentration 13.7 g/dl, and white cell count 6 x 10^9/l (6600/μl); distribution 62% polymorphs, 24% lymphocytes, and 14% monocytes. Cimetidine was stopped but prednisolone 10 mg continued. The figure shows the subsequent rise in the platelet count. Examination of the bone marrow five days after admission detected an increased proportion of megakaryocytes, consisting chiefly of mature forms.

Tests for platelet agglutinins and incomplete complement-fixing platelet antibodies both with and without the addition of cimetidine detected no abnormalities.

After 18 months the patient remained well with no recurrence of purpura. His platelet count is now 193 x 10^9/l (193 000/μl), similar to that found on presentation (see figure).

Comment

The American Food and Drug Administration studied 26 cases of haematological abnormalities (usually granulocytopenia) in about 1·3 million patients treated with cimetidine.3 In many cases the drug was exonerated or the data were insufficient. The other cases were complicated by factors such as renal failure, septicaemia, and treatment with cytotoxic drugs. Complicating factors are also apparent in other reported cases of thrombocytopenia associated with cimetidine treatment. Two patients4 5 also had large-bowel cancer and a third6 was an alcoholic with bleeding varices who evidently had had thrombocytopenia before taking cimetidine; after portacaval shunting he developed respiratory failure and subsequently renal and hepatic failure.

In the present case the appearance of severe thrombocytopenic purpura was temporarily related to the administration of cimetidine and reversed when cimetidine was stopped without altering the dose of prednisolone. The association with sarcoidosis is particularly interesting because this is a recognised though rare cause of thrombocytopenia, which may prove fatal if not treated with steroids or by splenectomy.4 Sarcoidosis alone is unlikely to have caused thrombocytopenia in the present case, since the platelet count was normal when the disease was most active and fell during remission. Cimetidine probably acted as a precipitant in a disease that predisposes the patient to autoimmune platelet destruction; the negative results of the antibody tests do not exclude this mechanism.

A recent report of autoimmune haemolytic anaemia during cimetidine treatment7 is relevant because this may also be associated with sarcoidosis. Increased peripheral destruction of blood cells sensitised by cimetidine (including leucocytes in some reported cases of neutropenia8) rather than bone-marrow toxicity may explain some of the haematological disturbances, particularly in predisposed patients. In view of the widespread use of cimetidine, the fact that there have been few reported cases of blood dyscrasia (none of them fatal) in uncomplicated peptic ulcer is reassuring.


(Accepted)

Department of Medicine, Westminster Hospital, London SW1P 2AP
A J ISAACS, BM, MRCP, senior registrar