Haemolysis complicating ibuprofen treatment

Use of the arylalkanoic anti-inflammatory drug ibuprofen has increased over the past eight years owing to its much lower incidence of serious toxic reactions than occurs with phenylbutazone or indomethacin. A very few cases of blood disorders have been noted,¹ but I can find no description of haemolytic anaemia in a patient receiving the drug.

I report a case of serious immunohaemolytic anaemia that developed during long-term treatment with ibuprofen.

Case report

A 69-year-old White woman (weight 72.4 kg) had a 16-year history of moderate intermittent pain and stiffness in the proximal interphalangeal joints, wrists, knees, and ankles. Her complaints varied over the years but the joints were never swollen or deformed, neither rheumatoid factor nor antinuclear antibodies were ever detected, and the erythrocyte sedimentation rate never exceeded 33 mm in the first hour. On several occasions she had been treated for a week to a few months with anti-inflammatory drugs such as phenylbutazone and aspirin without any toxic effects. She had last received treatment a few years before the following episode occurred.

In February 1976 the patient had a moderate relapse of symptoms and for the first time was treated with ibuprofen, 400 mg three times daily. For several months no discomfort or toxic reactions occurred. Then in September, after eight months of continuous treatment, there was an insidious onset of malaise, fatigue, and chills, which became increasingly prominent. A month later she was admitted to the medical ward.

On admission she had no sign of joint deformities but was anaemic and jaundiced, and had a temperature of 38.7°C. Her spleen was enlarged 5 cm below the costal margin. Laboratory investigations gave the following results: haemoglobin 5.4 g/dl; mean cell volume 102 fl (102 μm^3); mean cell haemoglobin concentration 32 g/dl (32%); serum iron concentration 40 $\mu\text{mol/l}$ (224 $\mu\text{g}/100\text{ ml}$); platelet count $242 \times 10^9/\text{l}$ (242 000/ mm^3); white cell count $16.7 \times 10^9/\text{l}$; reticulocytes 28%; serum bilirubin 113 $\mu\text{mol/l}$ (6.6 mg/100 ml); serum lactate dehydrogenase 2450 (normal 100-300) U/l. Bone marrow showed severe erythroid hyperplasia with a myeloid to erythroid ratio of about one. Peripheral blood smear showed anisocytosis and poikilocytosis. Osmotic fragility test showed median corpuscular fragility at 0.55% NaCl. LE cells were not detected; antinuclear factor test was moderately positive; complement fixation and cold agglutinin tests for *Mycoplasma pneumoniae* were negative; and streptococcal antibody tests were negative. Erythrocyte folate and serum vitamin B₁₂ concentrations were normal. Direct Coombs test was moderately positive; indirect Coombs test was negative. Ham and Crosby and Donath-Landsteiner tests were negative. "Incomplete" erythrocyte antibodies not related to blood types were detected in the serum but were not further investigated. Spontaneous haemolysis occurred at 37°C. Microscopical examination of the urine sediment showed numerous haemoglobin crystals. Serum creatinine was normal.

Ibuprofen was withdrawn on admission and replaced with prednisone

80 mg daily. The haemolysis slowly diminished. The reticulocytes reached 85% on the fifth day, and serum bilirubin 195 $\mu\text{mol/l}$ (11.4 mg/100 ml) on the 12th day. The haemoglobin began to rise on the 19th day. Twenty-three days after admission the reticulocytes were 2.2%, serum bilirubin was 51.3 $\mu\text{mol/l}$ (3.0 mg/100 ml), and haemoglobin was 11.3 g/dl. That day the patient developed severe pain, and cholelithiasis was diagnosed. Cholecystectomy was performed. In the postoperative period prednisone was discontinued and she received ampicillin, colistin, lincomycin, cephalothin, nitrofurantoin, frusemide, and phenothiazines without any sign of haemolysis.

Comment

Salicylate-like anti-inflammatory drugs such as phenylbutazone, indomethacin, and mefenamic acid have long been known to have serious toxic effects on haemopoiesis. Immunohaemolytic anaemia has also been reported,² though primarily in patients given mefenamic acid.³ Newer salicylate-like anti-inflammatory drugs, such as the arylalkanoic acids, however, cause few serious toxic reactions. Ibuprofen is one of the most widely used of these drugs, and though it may cause bone marrow depression¹ it has apparently never before been associated with immunohaemolytic anaemia.

In the present case there was strong evidence of a causal relation between ibuprofen and the immunohaemolytic anaemia. According to the patient and the family doctor she had not received other drugs for several months before admission. Furthermore, she had never had haemolytic anaemia or allergic reactions. The laboratory findings were consistent with immunohaemolytic anaemia, and the cessation of haemolysis when the drug was stopped and the absence of recurrence during and after the steroid treatment confirmed this.

The data do not conclusively indicate the type of haemolysis in this patient; but the chemical similarity of ibuprofen to mefenamic acid, which causes immunohaemolytic anaemia of the methyl-dopa type,³ the onset of haemolysis after eight months of continuous treatment, the positive direct Coombs test, and the positive antinuclear factor test suggest an autoimmune haemolytic type.

Though ibuprofen seems to cause few toxic reactions, long-term treatment should probably be given with caution. Whether the direct Coombs test will become positive during long-term treatment, as sometimes occurs with methyl-dopa, remains to be established, and only further study will show its value in predicting haemolysis.

¹ Cuthbert, M F, *Current Medical Research and Opinion*, 1974, 2, 605.

² Williams, J W, *et al*, *Hematology*, p 507. New York, McGraw-Hill, 1973.

³ Scott, G L, *et al*, *British Medical Journal*, 1968, 3, 534.

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SHORT REPORTS

Successful treatment of myocardial perforation and tamponade after temporary endocardial pacing

Temporary endocardial pacing for conduction defects after myocardial infarction is a relatively low-risk procedure in a high-risk condition.¹ Though tamponade from perforation of the right ventricle by the pacing electrode is a surprisingly uncommon complication, it should not be forgotten, as it is remediable.

Case history

A previously asymptomatic 48-year-old man was admitted to the coronary care unit with severe central chest pain radiating to both arms. Electrocardiography disclosed acute inferior cardiac infarction. On examination he was not shocked and had sinus rhythm of 80 beats/min, blood pressure of 120/80 mm Hg, normal heart sounds, and clear lung fields. Investigations showed: creatinine phosphokinase 611 units; ESR 50 mm in first hour; white cell count $11 \times 10^9/\text{l}$ (11 000/ mm^3).

There were no initial complications, and after 48 hours he was sent to a general ward on no specific drug treatment. The next day his pulse rate suddenly fell to below 60 beats/min and his blood pressure to 80/50 mm Hg. An electrocardiogram showed complete heart block. A No 5 USCI bipolar pacing catheter was inserted via a brachial vein into the apex of the right ventricle and satisfactory demand pacing established. For the next 48 hours his condition was stable (blood pressure of 120/80 mm Hg), but the position of the pacing electrode had to be adjusted twice.

Two days after the pacing electrode was inserted he suddenly went into ventricular fibrillation. After a 200 joule DC shock the rhythm reverted to that of heart block, with satisfactory pacing and cardiac output.

Thirty minutes later he had a further episode of ventricular fibrillation but this time cardioversion resulted in asystole. He was intubated and given external cardiac massage. Electrical pacing was established but with no cardiac output. Ventricular fibrillation recurred at frequent intervals for the next 20 minutes, despite adequate lignocaine treatment. Repeated DC shocks resulted in asystole and each time electrical pacing was established, but with no cardiac output.

Three reasons for these events seemed possible: a wide extension of the infarct; a massive pulmonary embolus; or cardiac tamponade. A diagnostic pericardial aspiration was performed from the xiphisternal approach, and with the removal of 70 ml of blood the peripheral pulses immediately reappeared, confirming the diagnosis of tamponade. A soft catheter was inserted into the pericardium with a Seldinger wire for continuous aspiration.

Sinus tachycardia with a good output ensued. The patient was transferred immediately to the operating theatre.

At operation about 50 ml of blood and clot was found in the pericardium. A large area of infarction was found, affecting the apex and inferior surface of the heart and the right ventricle. A hole 0.5 cm in diameter on the anterior surface of the right ventricle within the area of infarction was discovered and repaired. The patient made a good recovery, had no neurological deficit, and is pain free and back at work. His postoperative ECG showed that the infarction had extended to affect traces V1, V2, and V3.

Discussion

Perforation of the right ventricle by a pacing wire is not uncommon. Usually, however, when the wire is withdrawn the hole is quickly sealed, with minimal leakage of blood.² In this case the perforation occurred through infarcted tissue and tamponade resulted.

Although solitary right ventricular infarction is rare,³ necropsy evidence suggests that extension of a left ventricular infarct into the right ventricle is not unusual.⁴

Although the amplitudes of the right ventricular electrogram are checked at the time of insertion of the pacing wire, subsequent extension of the infarct into the area around the tip of the electrode may go undetected if satisfactory pacing is observed clinically. Tamponade is a rare complication of temporary pacing but should be remembered, especially if there is a sudden deterioration from satisfactory pacing and in spite of electrical activity no cardiac output is recorded.

We are grateful for the help of the intensive care and thoracic theatre nursing staff. Dr George Harwood performed the neurological assessment and Drs Jennifer Page and S Scott gave anaesthetics. We thank Dr W Mahon and Mr B Moore for permission to report this case.

¹ Chatterjee, K, *et al*, *Lancet*, 1969, 2, 1061.

² Meyer, J A, and Millar, K, *Annals of Surgery*, 1968, 168, 1048.

³ Kherdekar, S, and Nevins, M A, *Journal of the Medical Society of New Jersey*, 1973, 70, 374.

⁴ Harnagan, C, *et al*, *British Heart Journal*, 1970, 32, 728.

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Gut lymphoma presenting simultaneously in two siblings

Primary intestinal lymphoma is rare outside the Middle East—there are about 10 cases per million a year. A few cases have been reported in members of the same family but these have presented in childhood or early adult life.^{1 2} We report two cases of gut lymphoma occurring in a middle-aged brother and sister who presented simultaneously.

Case reports

Case 1—A 51-year-old woman presented in September 1976 with weight loss, progressive abdominal distension, vomiting, and anorexia. Examination showed ascites but no enlargement of the abdominal organs. Routine haematological and biochemical investigations and chest radiography gave normal results, and cytology of the ascitic fluid was negative. At laparotomy a large irreducible ileocolic intussusception was found, caused by a tumour, and a right hemicolectomy was performed. Histology showed a malignant lymphocytic lymphoma of diffuse small cell type affecting ileum, colon, and lymph nodes (see figure). A sternal marrow smear also showed infiltration by a well-differentiated lymphoma. A lymphangiogram was attempted but was technically unsatisfactory. Xylose and vitamin B₁₂ absorption were normal, and examination of faeces showed no evidence of steatorrhoea. Serum calcium concentration was low initially—2.02 mmol/l (8.1 mg/100 ml)—and has remained low—2.05 mmol/l (8.2 mg/100 ml). Serum albumin concentration, also low at presentation (16.2 g/l), has returned on chemotherapy towards normal—34.6 g/l. This patient is being treated with intermittent chlorambucil and prednisolone and is doing well.

Case 2—A 54-year-old man was admitted to hospital just two weeks after his sister (case 1). He had a three-month history of weight loss, constipation, bleeding per rectum, and tenesmus. On rectal examination a large tumour was easily palpable. Routine haematology, biochemistry, and chest radiography results were normal. At laparotomy the lesion was found to be inoperable and an end colostomy was performed. Biopsies taken at operation showed a diffuse lymphocytic lymphoma of mixed small and large cell type (see figure). Sternal marrow was normal and a lymphangiogram was contraindicated owing to postoperative pulmonary atelectasis. The serum calcium and serum albumin concentrations were low initially—2.04 mmol/l (8.2 mg/100 ml) and 25.5 g/l—and have subsequently returned to normal—2.28 mmol/l (9.1 mg/100 ml) and 42.4 g/l. A xylose absorption test gave a low result, though examination of faeces did not show any appreciable steatorrhoea. This man is being treated with pulses of cyclophosphamide, cytarabine, vincristine, and prednisolone. After an initial deterioration he is now responding to treatment.

Histological appearances of lymphocytic lymphoma. Above: Case 1, diffuse small cell type. Below: Case 2, mixed small and large cell type. ($\times 300$.)

To establish any common immunological, genetic, or familial factors various investigations were performed. Serum immunoglobulin concentrations were normal in both cases. An immunoperoxidase method failed to detect immunoglobulins in either tumour, and results of routine chromosomal analyses of peripheral white blood cells were normal. Virological screening of the patients, however, disclosed that both had a significant IgG titre to EB virus ($\log_2 5$ and $\log_2 7$), indicating past infection. The brother was said to have had malaria during the war but this could not be confirmed serologically. There was no family history of note and the patients had not lived in the same house for many years.

Comment

Smith and Pike³ warn that anecdotes of space-time clusters are not statistically meaningful as they may occur by chance; their value is