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 μmol/l (224 μg/100 ml); platelet count 242×10^9/l (242 000/mm^3); white cell count $16{\cdot}7 \times 10^9$/l; reticulocytes 28%; serum bilirubin 113 μmol/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 B_{12} 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 μmol/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 μmol/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 depression[1] 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 methyldopa 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 autoimmunohaemolytic 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 methyldopa, 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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Department of Medicine, Slagelse Hospital, 4200 Slagelse, Denmark
STIG KORSAGER, MD, specialist in internal medicine

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 11×10^9/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.