

Agranulocytosis and aplastic anemia possibly due to ibuprofen

To the editor: We wish to report a case of agranulocytosis and aplastic anemia possibly due to ibuprofen (Motrin, Upjohn), which we recently encountered. Except for "sporadic abnormalities of white blood count",¹ no hematologic complications appear to have been reported with the use of this drug.

An 82-year-old woman had been a resident of a home for the aged for almost 4 years, requiring general nursing care because of severely disabling joint disease.

Her joint complaints had started about age 50 and she had since been treated primarily with salicylates. Knees and shoulders had been most severely affected and she had received at least one intra-articular injection of dexamethasone in the shoulder; earlier that year, 1971, she had received a 1-week course of phenylbutazone without any apparent undesirable side effects.

The clinical and radiographic appearance of her joints strongly suggested rheumatoid arthritis. Her arthralgia had never had the typical features of acute gout. Degenerative changes were evident radiographically in the cervical and lumbar spine but did not appear to be producing symptoms.

A summary of selected laboratory data and therapy is shown in Fig. 1. The erythrocyte sedimentation rate had been moderately elevated between 1971 and 1974 (33 to 89 mm/h) but the latex fixation test had repeatedly been negative. Total serum protein value and electrophoresis findings were normal, and search for LE cells was negative at least twice. Serum uric acid values varied widely (3.0 to 8.7 mg/dl), probably the combined result of varying doses of salicylates and progressive renal insufficiency (serum urea nitrogen values, 22 to 32 mg/dl).

Abdominal distress had been a recurring complaint for at least the last 4 years and salicylates had been suspected as the

cause. A variety of antacids had been used to control this, and on Feb. 25, 1975 acetaminophen had been substituted for salicylates to avoid further gastric irritation. This provided less effective analgesia, and 1 week later ibuprofen therapy was introduced, at 600 mg/d, but it was apparently of no benefit.

Mild sideropenic anemia had been evident since at least 1971. Because of associated mild intermittent rectal bleeding sigmoidoscopy and radiography of the upper and lower intestine were performed; only diverticulosis coli and hiatus hernia with reflux were revealed. The bleeding was attributed to obvious hemorrhoids, and iron therapy was initiated with a series of injections of iron sorbitex (Jectofer) and continued with ferrous succinate, then ferrous sulfate and ferrous gluconate. No iron was given after Mar. 25, 1974. No appreciable improvement in hemoglobin concentration or hematocrit occurred except for a mild increase between April and September 1974 (Hb values, 10.7 to 12.0 g/dl; Hct., 35 to 37%); values then subsided to their previous range (Hb, 9.4 to 11.3 g/dl; Hct., 29 to 35%). Hematologic studies were repeated at approximately monthly intervals throughout this time, and between July 2 and Sept. 3, 1975 an abrupt decrease in leukocyte count was noted (from 4.5 to $2.6 \times 10^9/l$). Previous leukocyte counts had ranged from 3.3 to $7.5 \times 10^9/l$ (average, $4.96 \times 10^9/l$), and since May 6, 1975 there had been a definite downward trend. Ibuprofen therapy was discontinued Sept. 9, 1975.

About Sept. 16, 1975 malaise, anorexia and a mild sore throat developed. One week later her oral temperature was noted to be elevated (38.6°C) and it remained so; she was therefore admitted to hospital. Leukopenia worsened during the final 24 hours of life and granulocytes virtually disappeared; the number of lymphocytes was noted to be $0.8 \times 10^9/l$ from a buffy coat count. Abnormal physical findings at this time were minimal and nonspecific. She was restless and stuporous, with tachypnea and tachycardia but normal

blood pressure. The tongue was dry but otherwise normal, and the pharynx was moderately red, with a mucoid, nonpurulent postnasal discharge. Indefinite inspiratory crepitations were heard at both lung bases, and a long-standing apical systolic murmur was unchanged. Because of obesity and reflex guarding, results of abdominal palpation were not definitive; there did not appear to be hepatomegaly but the spleen was palpable to some observers. Lymph nodes were not enlarged and there was no purpura.

Routine laboratory tests revealed hyponatremia (serum sodium value, 127 mmol/l) and hypochloremia (serum chloride value, 89 mmol/l), with normal serum potassium value (4.6 mmol/l) and CO_2 content (25 mmol/l). Mild azotemia (serum urea nitrogen value, 31 mg/dl) was noted; values were unchanged from those observed over the previous 2½ years. Urinalysis disclosed moderate proteinuria but only occasional leukocytes, and urine culture was sterile. Cultures of blood yielded only *Staphylococcus epidermidis*, indicating contamination from the skin. No abnormal opacifications were seen on lung radiographs.

The severe leukopenia was thought to be evidence of a drug reaction, and all medications but digoxin were discontinued on Sept. 23. Digoxin had been used continuously since June 1972 for heart failure, the consequence of an acute myocardial infarction. Other agents withdrawn included furosemide (initiated in June 1972) and potassium chloride.

Her condition deteriorated rapidly, with declining level of consciousness and increasing dyspnea, and she died Sept. 24, about 48 hours after admission to hospital, no specific therapy having been instituted. No autopsy was done.

This case has been reported to the drug adverse reaction program of the health protection branch of Health and Welfare Canada.

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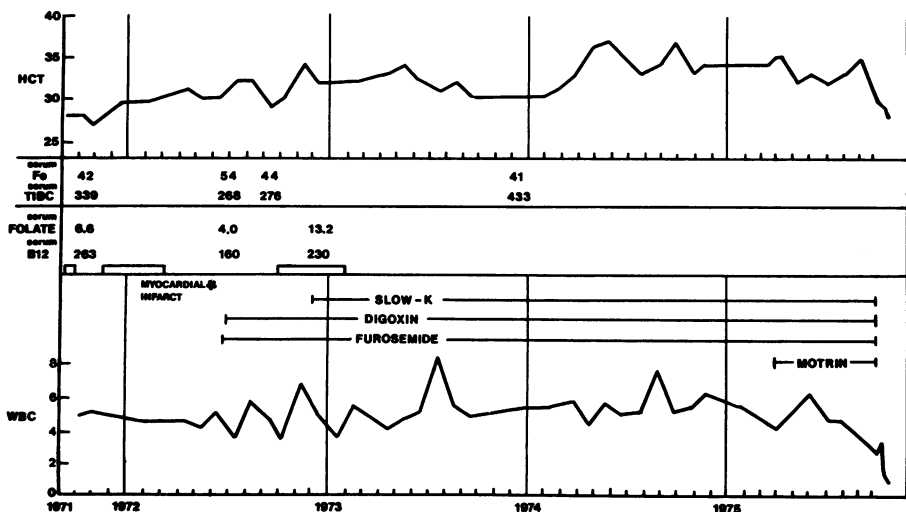


FIG. 1—Selected laboratory data and therapy over 4-year period in elderly woman with severely disabling joint disease. Values are given in the following units: hematocrit, %; serum iron, µg/dl; serum total iron-binding capacity, µg/dl; serum folate, ng/ml; serum B₁₂, pg/ml; leukocyte count, x 10⁹/l.

Reference

1. Motrin, in *Compendium of Pharmaceuticals and Specialties*, 10th ed, ROTENBERG GN, HUGHES FN (eds), Toronto, Can Pharm Assoc, 1975, pp 451-52

Constrictive pericarditis and pericardial calcification with positive histoplasmin skin test

To the editor: *Histoplasma capsulatum* was first reported as the etiologic agent of an acute, disseminated, fatal disease in 1906 by Darling.¹ In 1955 Billings and Couch² described two patients with pericardial calcification and histoplasmin sensitivity and suggested that *H. capsulatum* might be the cause of the pericardial disease.

Constrictive pericarditis is an uncom-

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References:

1. Cullen, S.I. *Curr. Ther. Res.*, 15, 5 243-247, May, 1973.
2. Eichman, M.L., Effect of Vehicle Composition on 'In Vitro' Release Rates of Betamethasone 17-Benzoate, March 29, 1971, R.R. #1, 922-0017.

Prescribing information:

Indications: Beben Gel is indicated for topical therapy of acute and chronic dermatoses.

It provides anti-inflammatory, anti-allergic and antipruritic activity in the topical management of corticosteroid-responsive dermatoses. These disorders include: psoriasis, eczematous dermatoses, lichen simplex chronicus and seborrheic dermatoses. In allergic or contact dermatitis, Beben Gel provides symptomatic relief.

Contraindications: Topical steroids are contraindicated in tuberculosis and fungal infections involving the skin, and in certain viral diseases such as herpes simplex, chickenpox, and vaccinia. Hypersensitivity to any of the components is also a contraindication.

Warning: The safety of topical corticosteroids during pregnancy or lactation has not been established. The potential benefit of Betamethasone benzoate, if used during pregnancy or lactation, should be weighed against possible hazard to the fetus or the nursing infant.

Precautions: Betamethasone benzoate is not for ophthalmic use, and it should be used with caution on lesions close to the eye.

Although hypersensitivity reactions have been rare with topically applied steroids, the drug should be discontinued and appropriate therapy initiated if there are signs of sensitivity.

In cases of bacterial infections of the skin, appropriate antibacterial agents should be used as primary therapy, with betamethasone benzoate used adjunctively to control inflammation, erythema, and itching. If a symptomatic response is not noted within a few days to a week, betamethasone benzoate should be discontinued until the infection is brought under control.

Significant systemic absorption may occur when steroids are applied over large areas of the body, especially under occlusive dressings. To minimize this possibility, when long-term therapy is anticipated, interrupt treatment periodically or treat one area of the body at a time.

Occlusive dressings should not be applied if there is an elevation of body temperature.

Adverse Reactions: When occlusive dressings are used; pustules, miliaria, folliculitis and pyoderma may occur. The following adverse skin reactions have been reported rarely with the use of topical steroids: dryness, itching, burning, local irritation, striae, hypopigmentation, atrophy and secondary infection.

Symptoms and Treatments of Overdosage: Percutaneous absorption of corticosteroids can occur especially under occlusive conditions. When large amounts of corticosteroid are absorbed, toxic effects may include ecchymoses of the skin, peptic ulceration, hypertension, aggravation of infection, hirsutism, acne, edema and muscle weakness, due to protein depletion. No specific antidote is available and treatment should be chiefly symptomatic.

Dosage and Administration: Apply to affected areas 2 to 4 times daily, as needed.

How Supplied: Betamethasone 17-benzoate 0.025% is supplied as:

Beben Gel, 15 gm and 60 gm tubes

Complete information available to physicians and pharmacists on request.

Warner/Chilcott

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mon disease: in a 10-year period only 79 cases were evaluated at the Mayo Clinic.³ We have recently studied two patients from the Ottawa area who were admitted to the cardiology service of Ottawa Civic Hospital in May 1974 with constrictive pericarditis and pericardial calcification.

Patient 1

A 51-year-old man was admitted to hospital with a 2-year history of shortness of breath on exertion and palpitation, and a 2-week history of swelling of both legs and abdominal discomfort. He had had no chest pain.

Blood pressure was 100/65 mm Hg; radial pulse rate was 100 beats/min and the rhythm, irregular. Jugular venous pressure was estimated at 6 cm H₂O; no a waves were noted in the pulse, the y descent was sharp and Kussmaul's sign was observed. No clubbing or cyanosis was noted. Pitting edema was detected in both legs. The first heart sound was loud, the second was split and a pericardial knock was heard at the apex. Coarse crepitations were heard at both lung bases. The liver was tender and palpable 4 cm below the right costal margin. Moderate ascites was noted.

Laboratory investigations yielded the following abnormal values: erythrocyte sedimentation rate (ESR), 55 mm/h; serum alkaline phosphatase, 190 IU/l; serum albumin, 2.8 g/dl; and total serum bilirubin, 2.4 mg/dl. A trace of albumin was detected in the urine. The electrocardiogram (ECG) showed atrial fibrillation, a ventricular rate of 86 beats/min and nonspecific ST-segment and T-wave changes. Apex cardiogram showed retraction of the apex during ventricular systole, with a large, early-diastolic outward motion. Chest radiographs in several views showed linear pericardial calcification and perihilar calcified spots. Tuberculin skin test with 5 TU of purified protein derivative (PPD) was negative but histoplasmin skin test with 0.1 ml of histoplasmin was strongly positive (14 mm of induration). Sputum cultures were nega-

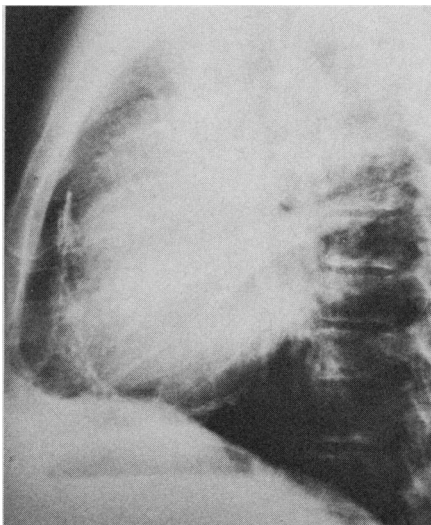


FIG. 1—Linear pericardial calcification in patient 2 preoperatively.

tive. The titre of complement-fixing serum antibodies to *H. capsulatum* was 1:4.

Patient 2

A 55-year-old man was admitted to hospital with a 2-month history of shortness of breath on exertion and a 1-month history of swelling of both legs and pain in the right hypochondrium. He had had no chest pain.

Blood pressure was 120/80 mm Hg; radial pulse rate was 120 beats/min and the rhythm, regular. Jugular venous pressure was estimated at 4 cm H₂O; the y descent was sharp and Kussmaul's sign was present. Pitting edema was noted in both legs. The apex beat was ill-defined. The first heart sound was normal but the second was split and a pericardial knock was heard at the apex. Coarse crepitations were detected at both lung bases. The liver was palpable 2 cm below the right costal margin and there was evidence of minimal ascites.

Laboratory investigations yielded the following abnormal values: ESR, 30 mm/h; serum alkaline phosphatase, 105 IU/l; serum albumin, 3.2 g/dl; and total serum bilirubin, 1.2 mg/dl. A trace of protein was detected in the urine. ECG showed atrial flutter (240 beats/min) with a 2:1 ventricular response, nonspecific ST-segment and T-wave changes and borderline low voltage. Chest radiography and fluoroscopy revealed pericardial calcification (Fig. 1). Tuberculin skin test with 5 TU of PPD was negative but histoplasmin skin test with 0.1 ml of histoplasmin was strongly positive (12 mm of induration). The titre of complement-fixing serum antibodies to *H. capsulatum* was 1:2.

Special investigations

Characteristic findings from cardiac catheterization in both patients were elevated mean right atrial pressure, M pattern of the right atrial pressure pulse and early diastolic dip, and elevated end-diastolic pressure in both ventricles. Pulmonary wedge, pulmonary artery, right ventricular end-diastolic, mean right atrial and superior vena caval pressures were identical in the two patients. Cardiac outputs were within normal limits. Coronary artery angiograms were normal.

Treatment

The two patients underwent pericardiectomy. Both required digoxin and diuretics during the immediate postoperative period. Much symptomatic improvement was observed in both patients during 6 months of postoperative follow-up. Histopathologic study and culture of pericardial tissue failed to demonstrate fungal growth.

The cause of calcification of the pericardium is obscure in many instances. In most cases, by the time bacteriologic and pathologic studies can be undertaken, evidence of specific infection or injury is not demonstrable. Pericardial calcification is seen in approximately half the patients with constrictive pericarditis. Chronic constrictive

Indications: Zaroxolyn (metolazone) is indicated in treatment of edema accompanying congestive heart failure; edema accompanying renal diseases and states of diminished renal function, including the nephrotic syndrome. Metolazone is also indicated to reduce blood pressure in the management of mild to moderate essential hypertension, either as the sole therapeutic agent or in combination with other antihypertensive therapy.

Contraindications: anuria, hepatic coma or pre-coma, and in cases of known hypersensitivity to metolazone and other sulfonamide derivatives.

Precautions: Patients receiving metolazone should be carefully observed and serum electrolytes monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatremia, hypochloremia and hypokalemia. Blood urea nitrogen, uric acid, and glucose levels should also be assessed during therapy. Hypokalemia, an ever present hazard with most diuretic therapy, will be more common in association with intensive or prolonged diuretic therapy, with concomitant steroid or ACTH therapy, and with inadequate electrolyte intake. The serum potassium should be determined at regular intervals and potassium supplementation instituted when indicated.

The clinical signs of electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting.

Metolazone may potentiate the effect of tubocurarine and decrease the arterial response to norepinephrine. On this basis it may be advisable to discontinue the drug at least 48 hours prior to elective surgery.

Special caution should be used in treating patients with severe hepatic disease since diuretics may induce metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When metolazone is used with other antihypertensive drugs, particular care must be taken, especially during initial therapy. Dosage of other antihypertensive agents, especially the ganglionic blockers and guanethidine, should be reduced. Hydralazine in therapeutic doses may interfere with the natriuretic action of metolazone.

Metolazone may be given with a potassium-sparing diuretic when indicated. In this circumstance, diuresis may be enhanced and dosages should be reduced. Potassium retention and hyperkalemia may result; the serum potassium should be determined frequently. Potassium supplementation is contraindicated when a potassium-sparing diuretic is given.

While not reported for metolazone, use of diuretics have on rare occasion been associated with pathologic changes in the parathyroid gland and with hypercalcemia and hypophosphatemia. Sulphonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. These possibilities should be kept in mind with use of metolazone.

Caution should be observed when administering the drug to patients with severely impaired renal function, since the drug is excreted primarily by the renal route.

Caution should be observed when administering metolazone to hyperuricemic or gouty patients. The drug exerts minimal effects on glucose metabolism; insulin requirements may be affected in diabetics, and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Until additional data have been obtained, metolazone is not recommended for patients in the pediatric age group.

Usage in Pregnancy: Since metolazone crosses the placenta and appears in cord blood, its administration to women of childbearing age requires that the potential benefits of the drug be weighed against its possible hazards to the fetus. The potential effects on the fetus include fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions which have occurred in the adult. However, teratologic studies in mice, rats and rabbits, conducted for three generations in rats, have not shown teratogenic effects in these animals.

Metolazone appears in breast milk. Thus it is possible that the effects of metolazone may occur in the newborn under these circumstances. If the use of metolazone is deemed essential for a nursing mother, the patient should stop nursing.

Adverse Reactions: Gastrointestinal reactions: constipation, nausea, vomiting, anorexia, diarrhea, abdominal bloating, epigastric distress, intrahepatic cholestatic jaundice, hepatitis.

Central nervous system reactions: syncope, dizziness, drowsiness, vertigo, headache.

Cardiovascular reactions: orthostatic hypotension, excessive volume depletion, hemoconcentration, venous thrombosis, palpitation, chest pain.

Hematologic reactions: leukopenia.

Dermatologic reactions: urticaria and other skin rashes.

Other reactions: dryness of the mouth, symptomatic and asymptomatic hypokalemia, hyponatremia, hypochloremia, hypochloremic alkalosis, hyperuricemia, hyperglycemia, glycosuria, increase in BUN or creatinine, fatigue, muscle cramps or spasm, weakness, restlessness, chills, acute gouty attacks.

Adverse reactions which have occurred with other diuretics, but which have not been reported to date for metolazone include: pancreatitis, paresthesias, xanthopsia, agranulocytosis, thrombocytopenia, aplastic anemia, purpura, photosensitivity, and necrotizing angitis (cutaneous vasculitis). These reactions should be considered as possible occurrences with clinical usage of metolazone.

Whenever adverse reactions are moderate or severe, metolazone dosage should be reduced or therapy withdrawn.

Dosage: Initial dosages: Mild to moderate essential hypertension: 2½ mg to 5 mg, once daily. Edema of cardiac failure: 5 mg to 10 mg once daily. Edema of renal disease: 5 mg to 20 mg, once daily. The daily dosage depends on the severity of each patient's condition, his sodium intake, and his responsiveness. Therefore, dosage adjustment is usually necessary during this course of therapy.

Supplied: Tablets, 2½ mg (pink), 5 mg (blue), and 10 mg (yellow).

Complete prescribing information available on request.

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pericarditis is thought to result from the healing of acute fibrinous or serofibrinous pericarditis;⁴ most cases are due to tuberculosis, but some are due to staphylococcal or pneumococcal infection.

It is unlikely that pericardial calcification due to histoplasmosis is a new entity, but it has probably often been overlooked. It is frequently difficult to differentiate from other types of calcification without histoplasmin skin testing.⁵ Brodsky and colleagues⁶ reported that skin tests were positive in 70 to 79% of residents in Delaware County, Ohio during an outbreak of histoplasmosis. The Ottawa Valley has been reported to be an area of high prevalence of skin-test sensitivity (A.G. Jessamine, Provincial Chest Clinic, Ottawa: personal communication, 1974) and positive titres of complement-fixing antibodies to *H. capsulatum* (S.E. Johnson, community health protection branch, Ontario Ministry of Health: personal communication, 1974). Complement-fixing antibodies appear in the blood about the 3rd week after pulmonary infection with this fungus. There is some evidence that the antibody titre in histoplasmosis is proportional to the severity of the infection; with recovery the antibodies gradually disappear from the blood.

A definitive diagnosis of histoplasmosis can be made only by isolating the fungus,⁷ and in our patients special stains failed to demonstrate any fungi in the pericardial tissue sections. However, in an area of high incidence of histoplasmosis, strongly positive histoplasmin skin tests suggest the diagnosis. Histoplasmin skin tests and complement-fixing antibody tests are valuable in recognizing acute pericarditis due to *H. capsulatum* and in determining the cause of pericardial calcification with constrictive pericarditis.

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