Medical Memorandum

Aplastic Anaemia Due to Phenylbutazone

Fatal agranulocytosis following phenylbutazone is now well recognized, but aplastic anaemia has been reported only by Leonard (1953), whose patient had previously received gold therapy. The occurrence of fatal aplastic anaemia is here reported in a patient who had not previously been exposed to any bone-marrow poison.

CASE HISTORY

A married woman aged 55 complained of pains in the back and various joints over a period of 10 years, and was put on phenylbutazone therapy by her general practitioner in March, 1953. She was also on thyroid, 2 gr. (0.13 g.) daily, from January, 1953, onwards, a diagnosis of myxoedema having been made at another hospital. Phenylbutazone was taken from March, 1953, until November, 1954, the dose at first being 200 mg. three times daily and subsequently 100 mg. three or four times daily. In November, 1954, she complained of bruising easily and of a rash "like blood blisters." She began to feel very weak. She was first seen in hospital when sent up for emergency admission on February 15, 1955.

On examination no objective evidence of joint disease was found and there was no subsequent complaint of the symptoms for which phenylbutazone was originally prescribed. The patient was extremely anaemic, with ecchymoses and widespread petechiae. Haemorrhages were present in the conjunctivae, mouth, and retinae.

There was no evidence of myxoedema, no enlargement of the liver, spleen, or lymph nodes, and the thyroid gland was not palpable. A blood count showed: haemoglobin, 6 g. per 100 ml.; red cells, 1,850,000; colour index, 1.15; white cells, 2,300 (39% polymorphs, 54% lymphocytes, 7% monocytes). The platelet count was 25,000. The sternal marrow was reported on by Dr. J. Davson as follows: "The marrow shows a considerable depression of the red-and-white-cell precursors. Most of the cells present are lymphocytes, reticulum cells, or plasma cells. The picture is that of an aplastic anaemia or panhaemocytopenia."

A course of treatment with cortisone acetate was given, 300 mg. daily for five days, 250 mg. daily for eight days, 200 mg. for a month, and gradual reduction over a further 10 days. After three weeks on cortisone there had been no significant change in the level of red cells, white cells, or platelets and no reticulocyte response, and transfusion treatment was accordingly started. The haemoglobin level was raised from 4 to 8.5 g., but subsequently fell again in spite of further transfusions. The platelet count varied between 5,000 and 40,000 per c.mm. and the white-cell count between 1,700 and 5,000, with polymorphs between 5% and 40%, the remaining white cells being normal lymphocytes and monocytes. Fresh crops of purpura and ecchymoses were appearing, and transfusions were made difficult by haemorrhage into the tissues at the site of venepunctures. The patient's condition deteriorated steadily, and she died following haemorrhage in the alimentary tract on July 27, 1955. She had received a total of 27 pints (15.4 litres) of blood by transfusion.

Post-mortem Findings (Dr. M. C. H. Dodgson).—The body was that of an obese hirsute middle-aged woman. There were severe aplastic changes with some focal haemorrhages in the marrow of the sternum, ribs, vertebrae, right ilium, and right femur; the lymph nodes were hypoplastic. Although deformities characteristic of rheumatoid arthritis were absent, the articular surfaces of the right knee-joint showed moderately severe osteoarthritic changes. Myocardium: fatty degeneration, epicardial and endocardial haemorrhages. Pleurae: bilateral small straw-coloured effusions with induration and congestion of the lungs. A lymph

node draining the left upper lobe contained an area of fibrocaseous tuberculosis, 0.5 cm. in diameter, a similar focus, 1 cm. in diameter, occurring in the lower pole of the right kidney. The left kidney and the remainder of the urinary tract appeared healthy. No macroscopic changes were noted in the brain. Pituitary, parathyroids, and ovaries appeared normal, whereas the thyroid was small, flat, and pale, and the adrenals showed cortical atrophy.

Histological Examination.—The bone marrow of the lumbar vertebrae showed osteoporosis with severe reduction of the haemopoietic tissue, the surviving red marrow, confined to the periphery of the vertebral body, being infiltrated with lymphocytes. Myocardium, kidney, and liver showed severe fatty changes, referable to the anaemia, although haemosiderin-laden phagocytes occurred in lymph nodes, spleen, and bone marrow. The lungs showed passive venous congestion and acute oedema.

COMMENT

Although there have been many reports of the toxicity of phenylbutazone, a review of which has been made by Mauer (1955), this drug is still used on a wide scale. Until recently authors reporting toxic effects, have merely urged caution in the use of the drug, and it has been suggested that it should be given only after full hospital investigation and assessment. Caution is, however, no safeguard against many of the lethal complications of phenylbutazone therapy. Gastric ulceration may occur in the absence of any previous dyspeptic history, and may prove fatal through haemorrhage or perforation. Regular white-cell counts are no safeguard against toxic granulocytopenia. Hypersensitivity reactions may occur in patients with no previous history of allergy or hypersensitivity to drugs. Fatal hepatic necrosis may occur, and there is no safeguard against this. The occasional occurrence of severe reactions unfortunately bears no relationship to dosage, so that avoidance of overdosage is no safeguard (Nassim and Pilkington, 1953; Leonard, 1953).

Phenylbutazone is chemically related to amidopyrine, the use of which has already been abandoned in this country. A suggestion that there might be a specific antirheumatic effect of the drug has received little support, and all the evidence points to its beneficial effect upon rheumatoid arthritis being entirely attributable to its analgesic action. Claims have been made that phenylbutazone is superior to aspirin as an analgesic, but there have been no controlled trials to establish this, particularly when aspirin is used in the manner recommended by the Medical Research Council and Nuffield Foundation report (1954). When these recommendations are followed recourse to phenylbutazone therapy need seldom be considered. Phenylbutazone produces an extremely high incidence and wide variety of toxic effects, many of which are potentially lethal. It is therefore considered to be a dangerous drug which should not be used for the treatment of non-fatal diseases, such as rheumatoid arthritis. This conclusion is in agreement with that reached by Fraser (1955) and is in contrast with the acceptance of the drug with reservations by previous authors, who have suggested that it should be used with caution. It is pointed out that caution provides little safeguard against the many different lethal side-effects.

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