Adverse Reactions to Sulphasalazine

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INTRODUCTION

Sulphasalazine is a drug which is the therapeutic mainstay in the prevention of recurrence of ulcerative colitis and is also used in the treatment of active disease. It consists of a sulphonamide (sulphapyridine) and a salicylate (5-amino salicylic acid) component with the latter being the active moiety in colitis. However it was originally developed as a treatment for rheumatoid arthritis (1) and in the past 3 years there has been a renaissance both locally and nationally in its use by rheumatologists as a second line agent in the treatment of rheumatoid arthritis (2,3) and to a lesser extent in ankylosing spondylitis. It is regarded as a safe drug when compared with the severe side effects reported with the other commonly used disease-modifying agents in rheumatoid arthritis such as gold and penicillamine.

We would like to add a note of caution to this view of sulphasalazine by reporting three cases of severe neutropenia in patients which occurred over a four month period between 1983 and 1984 in the Bristol Royal Infirmary in association with this drug.

CASE 1

A 63 year old retired barmaid with active rheumatoid arthritis was treated with sulindac 400 mg daily, chlormezanone 200 mg nocte and sulphasalazine 1 g daily. Haemoglobin was 11.2 g/dl and neutrophil count was 5.3×10^9/l. Seven weeks later she was admitted with dental and mouth sepsis and septicaemia. Blood cultures grew a coliform organism and she was treated with broad spectrum antibiotics. Total white cell count on admission was 0.5×10^9/l with no neutrophils. Sulphasalazine was discontinued and one week later her neutrophil count had risen to 1.3×10^9/l with clinical recovery.

CASE 2

A 69 year old man presented with a four week history of severe bloody diarrhoea, weight loss and abdominal pain. Haemoglobin was 12.6 g/dl, white cell count 10.9×10^9/l with 57% neutrophils, serum albumin 29 g/l and plasma viscosity was elevated at 1.91 cp. A diagnosis of ulcerative colitis was confirmed histologically and a barium enema showed this to be total. He was treated with oral and rectal prednisolone and commenced on sulphasalazine 4 g daily eight days after admission. His course was complicated by a transient ischaemic attack and an arterial embolus to the left foot which improved with conservative measures. He was eventually discharged six weeks after admission taking a reducing course of oral prednisolone, prednisolone enemata, aspirin and sulphasalazine 3 g daily. Six days later he was re-admitted with a gram negative septicaemia, severe oral candidiasis and a perianal abscess, incision of which failed to show pus. Total white cell count was 1.0×10^9/l with no neutrophils. Despite treatment with antibiotics, granulocyte transfusion and withdrawal of sulphasalazine he died four days later. A postmortem showed quiescent ulcerative colitis.

CASE 3

A 76 year old woman was admitted with a sudden onset of bloody diarrhoea. Sigmoidoscopy revealed a florid proctitis and radiology and rectal biopsy confirmed the diagnosis of ulcerative colitis. Haemoglobin was 11.0 g/dl and white cell count was 4.5×10^9/l with 72% neutrophils. Her condition improved with sulphasalazine 4 g daily and prednisolone 10 mg daily on which she was discharged. She also continued her previous drug treatment of imipramine, benzhexol and trifluoroperaxine. She was re-admitted two weeks later with a haemoglobin of 8.7 g.dl, a neutrophil count of 1.1×10^9/l and 8.2% reticulocytes. Haemolysis continued with reticulocytes rising to 15% and a blood film showing nucleated red cells and spherocytes. A Coombs test was negative and glucose 6 phosphate dehydrogenase levels were within normal limits. Neutrophils fell to 0.25×10^9/l. Sulphasalazine was discontinued six days after admission and haematological indices returned to normal.

DISCUSSION

Drug induced neutropenia is uncommon with an incidence in Sweden of 0.009%[4]. This systematic survey showed sulphonamides to be one of the most frequent offenders and responsible for five out of nine fatal cases. There are many reports of sulphasalazine associated agranulocytosis in the literature (5,6,7) but the occurrence of three cases together is highly unusual, although no common link among our patients is apparent. One of the cases also developed haemolysis which has been related to high sulphapyridine levels (8) and slow acetylator status (9). Neutropenia is thought to be due to immunological rather than directly toxic mechanisms (10).

In the treatment of ulcerative colitis new methods are being developed for the delivery of 5-aminosalicylic acid, the active moiety of sulphasalazine, to the colon (11,12) without the presence of the sulphonamide component.

However the active component of sulphasalazine in rheumatoid arthritis is thought to be the sulphonamide moiety (13), so the newer agents developed for ulcerative colitis which exclude this component will be of no value in this condition. If sulphasalazine is to be commonly used in rheumatoid arthritis than a widespread awareness of its potentially lethal side effects is essential. A wise precaution would be to warn all patients to

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After demobilisation he became deputy Medical Superintendant in Weston super Mare and in 1948 was appointed Consultant General Physician to Ham Green Hospital and worked there continuously until his retirement in 1976.

With the wide experience he had had before, during and after the war Jimmy was a classic example of the devoted whole time Medical Superintendant who could turn his skills to practically every branch of clinical medicine and surgery. His appointment to Ham Green coincided with the effective chemotherapy for most of the major infectious diseases and he had the thrill and pleasure of taking a major part in the virtual eradication of many of these previously dreaded conditions. But other challenges arose and Jimmy tackled them with skill and ingenuity; not only was he a wise physician but he had a remarkable mechanical aptitude.

In the 1950s with the upsurge of poliomyelitis he pioneered the development of assisted positive pressure respiration and built most of the early apparatus himself with the help of a local garage engineer. In 1959 he published in the Lancet the second account of such treatment in the UK—the first having appeared in the same journal only the week previously from Oxford. He personally performed nearly 250 tracheotomies for diphtheria, poliomyelitis and other forms of respiratory failure and in 1962 he carried out the first renal dialysis to be performed in the Bristol Clinical Area on a patient with renal failure due to drinking antifreeze. The first patient to be accepted for maintenance dialysis is still alive and in 1968 Humphrey White performed the first renal transplant in Bristol on one of his patients.

During his years at Ham Green Jimmy was virtually never off duty by day or by night and was an inspiration to his junior staff for his dedication and the standard of medicine which he set. He was greatly admired by all for his modesty and his devotion to his patients and his opinion was eagerly sought by consultants and general practitioners alike. For 17 years he was treasurer of the Bristol Medico-Chirurgical Society and his Presidential Address in 1972 was on "Edward Jenner—a great Englishman". It was very appropriate that he was a founder member of the Jenner trust set up in Bristol in 1967.

In 1968 Jimmy had a stroke from which he made a reasonable recovery but in 1982 his wife Phyl also suffered a stroke, thereafter they lived quietly in retirement until his peaceful end. He is survived by Phyl and their daughter Judy.

A. T. M. Roberts.

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report sore throats or other symptoms of infection immediately during treatment.

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ACKNOWLEDGEMENT

Miss Victoria Blake for secretarial assistance.