Medical Memoranda

Folic-acid Antagonists in Treatment of Psoriasis

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Folic-acid antagonists have been used in the treatment of psoriasis since 1951 (Gubner *et al.*, 1951). They presumably act by reducing the greatly increased mitotic activity of the epidermis in this disorder (Van Scott and Reinertson, 1959); other rapidly dividing tissues such as the leucopoietic system and the gastro-intestinal mucosa are also affected, but by limiting the dose a selective effect on the psoriatic epidermis may be achieved. Patients need to be carefully chosen, and require close clinical observation as well as repeated blood counts and checks on renal and hepatic function. This therapy has already been well tried in the U.S.A., where at least 5,000 cases of psoriasis have been treated (Rees *et al.*, 1964), and is gaining popularity here (Ryan *et al.*, 1964). Toxic reactions such as mouth ulceration, gastro-intestinal symptoms, and depressed blood counts do occur, and give a warning that treatment must cease; so far three deaths have been reported (Rees *et al.*, 1964).

It is the intention of this report to add to the limited evidence of the danger of this therapy, and to dispel any complacency that may exist in prescribing folic-acid antagonists for psoriasis. From a series of only 10 patients the following two suffered serious reactions from methotrexate.

CASE 1

A man aged 62 began to have psoriasis on his legs and arms at the age of 55; when 60 he was treated with topical steroids, and the psoriasis became widespread and pustular. He was very ill with recurrent high fevers, which were attributed to exacerbations of his pustular psoriasis as no other cause could be found. Systemic steroids were of no benefit. A good response was obtained first with aminopterin (several courses of 0.5 mg. a day for five days), later followed by eight courses of methotrexate (2.5 mg. a day for five days) over a period of five months; transient mouth-ulceration was the only complication, and temporarily interrupted treatment. During this time he underwent an emergency transurethral resection of his prostate and subsequently developed a severe Friedländer's pneumonia, which necessitated withdrawal of the methotrexate. Eventually a sufficient remission occurred to permit his return home.

Unfortunately, within a month his pustular psoriasis relapsed and he became seriously ill. On admission he had large areas of pustules with crusted lesions on his trunk and limbs; he had a fever of 101° F. (38.3° C.), some dyspnoea, and ankle oedema. A chest radiograph showed opacities in both upper zones, but these had not altered since his apparent recovery from pneumonia four months previously. Haemoglobin was 11 g./100 ml., white-cell count 9,900/c.mm. (neutrophils 80%, lymphocytes 13%, monocytes 6%, eosinophils 1%), and platelets 415,000/c.mm.; Westergren E.S.R. 115 mm. per hour (this had always been high, and was assumed to be due to his pustular psoriasis).

Methotrexate 5 mg. a day was started. On the fifth day his white-cell count was 10,200/c.mm. and the dose was reduced to 2.5 mg. a day. His skin began to weep over large areas. On the eighth day of treatment mouth ulcers appeared and the peripheral blood picture showed only 550 white cells and 8,700 platelets per c.mm. He became hypotensive, oliguric, and very weak. Resuscitative measures, including folic acid and antibiotics, were of no avail and he died.

At post-mortem examination the lungs were very oedematous and contained little pus, but *Klebsiella pneumoniae* was grown from

swabs taken from several parts of the lungs. The kidneys showed renal tubular necrosis.

CASE 2

A man aged 65 began to have psoriasis when he was 31, and ever since then it has involved large areas of his trunk and limbs. Local treatment failed to control the psoriasis, and methotrexate was prescribed. In 1952 a duodenal ulcer had been diagnosed, and was treated medically with apparent healing after four months; since then he had suffered only occasionally from mild dyspepsia.

During his eighth course of methotrexate he developed mouth-ulceration and the tablets were stopped; the ulcers healed by the fourth day. The next day, although pain-free, he passed a large melaena stool, and his haemoglobin fell from 11 to 6 g./100 ml., with resultant mild congestive heart failure. After 3 pints (1.7 litres) of blood his haemoglobin rose to 10 g./100 ml., and with parenteral iron reached 13 g. in four weeks. After resuscitative measures a barium-meal examination showed a duodenal ulcer. He made an uneventful recovery.

COMMENT

In the first case it was felt that only treatment with methotrexate would benefit him. The patient was very ill, and even without the leucopenia the stress of renal tubular necrosis and pneumonia would probably have been fatal, but it cannot be denied that it was a probable factor in promoting this result. No evidence of internal haemorrhage was found, and it would appear that the leucopenia was the more significant toxic reaction.

In the second case the coincidence of the haemorrhage and the therapy is suggestive of a causal relationship. The white cells and platelets were not depressed in this case nor was erythropoiesis retarded; the drug is presumed to have inhibited the natural regeneration of the gastro-intestinal mucosa over the ulcer site. Admittedly the mouth ulcers had healed before the haemorrhage began; it remains possible that the haemorrhage may have been only a coincidence. Haemorrhage from peptic ulcers is not a common complication of folic-acid antagonist therapy except in leukaemia.

There is a place for methotrexate in the treatment of intractable psoriasis, but these two cases demonstrate that even with adequate supervision this therapy can be very dangerous. The decision to treat a benign dermatosis such as psoriasis with as dangerous a drug as methotrexate must be taken with as much care and consideration as is accorded to the decision to employ systemic steroid therapy.

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