Photosensitivity from Nalidixic Acid [*Abridged*]

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Seven patients with photosensitivity from nalidixic acid seen since 1968 were reported. All were females and all showed blisters on the dorsa of the feet; the lower legs and the dorsa of the hands were also frequently affected. The eruption frequently started when the patient was on holiday and a high level of ambient sunlight seemed to be more important than the length of time that the drug had been taken. Blisters often continued to appear for several months after the drug had been stopped and fragility of the skin was seen in 4 patients. Porphyrin excretion was normal in all patients. Photopatch tests were performed in 3 patients and were negative.

Skin tests with narrow waveband artificial ultraviolet were carried out in all patients and reactions to longwave u.v. were detected in 3 of them. Two volunteers took the drug in a dose of 4 g daily for one week and at the end of this time immediate erythematous reactions to longwave u.v. were present in both volunteers, the significance of which is uncertain. Definite abnormal delayed erythematous reactions to a broad spectrum long u.v. source was detected in both volunteers after the drug had been taken. Further investigations with this source in another volunteer are being undertaken.

Although the mechanism underlying the photosensitivity from nalidixic acid is unknown, the eruption usually presents a very characteristic clinical picture. Our experience suggests that patients may continue to take the drug providing that they avoid direct sunlight on the skin. It would probably be wise to give similar advice to all patients taking the drug.

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Azathioprine in Psoriasis

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Psoriasis is characterized by proliferation of epidermal cells with greatly increased rate of cell turnover. The most successful treatments of psoriasis reduce the epidermal turnover time by chemical or physical means. Cell poisons such as mercury, arsenic, phenolic compounds, methotrexate, azathioprine and corticosteroids all help in the therapy of psoriasis.

Some cytotoxic compounds such as corticosteroids and azathioprine have an immunosuppressive action as well as interfering with nuclear protein synthesis, and it may be impossible to distinguish which of these two actions is responsible for a therapeutic response.

The use of cytotoxic drugs, of the type developed for cancer therapy, was a major advance in the management of severe psoriasis, and methotrexate especially appeared to be an effective drug with high patient tolerance and low incidence of complications. From 1951 when Gubner *et al.* described its use in psoriasis, dermatologists gradually became more familiar with the efficient use of the drug, but in 1964 O'Rourke & Eckert reported serious hepatic changes in a psoriatic patient who received methotrexate. This confirmed a similar finding in leukæmic children treated with the same drug (Colsky *et al.* 1955). Since this initial report, the hepatotoxic action of methotrexate has been reported increasingly often when this form of toxicity is specifically sought (Dahl *et al.* 1971, 1972).

The value of other cytotoxic drugs in relationship to their toxic actions has therefore been studied in psoriasis, and the present project was undertaken to evaluate azathioprine in the management of severe psoriasis, taking particular note of evidence suggesting liver damage caused by the drug.

Azathioprine is an imidazolyl derivative of mercaptopurine and *in vivo* 90% is converted into 6-mercaptopurine and 10% excreted unchanged in the urine. About half of the mercaptopurine is excreted within twenty-four hours but the therapeutic action continues long after the drug has been cleared from the blood. Mercaptopurine is an analogue of hypoxanthine and a competitive inhibitor. The ribonucleotide of hypoxanthine is the first biosynthetic purine and the core of all purine metabolism. By interference with this metabolism DNA and RNA synthesis is inhibited.

Toxic actions of the drug include bone marrow hypoplasia, hepatotoxicity, gastrointestinal upsets, reduced resistance to infection, malignant tumours and teratogenicity. The usual dose given orally is 1–5 mg/kg per day.

Patients and treatment: Twenty-nine patients with an average age of 51 years (range 23–79 years) were studied. Sixteen men and 13 women formed the group, of whom 6 were under 40 years. Women of childbearing age were advised to remain on a contraceptive pill throughout the period of medication.

All patients had severe psoriasis which had failed to respond to simpler treatment or to methotrexate. Cases who were taking systemic

corticosteroids to control their disease were transferred to azathioprine. The dose prescribed was the smallest required to control the disease, but usually 2–4 mg/kg per day was given, with an upper limit of 300 mg/day in any patient.

The duration of treatment ranged from 2 weeks to 31 months, with a mean therapy duration of 12 months in 20 cases who had follow-up liver biopsies.

Results: A good clinical response was obtained in 16 patients (55%) in whom more than three-quarters of the psoriasis cleared. Three patients became completely free of psoriasis and stopped the drug. An improvement with half to three-quarters of the psoriasis cleared was recorded in another 3 patients; thus 19 patients (65%) benefited significantly from the drug. Seven patients derived no benefit and 3 patients had to stop treatment due to side effects; thus treatment failed in 10 patients (35%).

Gastrointestinal upset, especially anorexia, nausea and occasionally diarrhœa and vomiting, was encountered in 12 cases. These symptoms tended to settle if the dose were divided and gradually increased over several weeks, rather than the full therapeutic dose being given at the onset of treatment.

Macrocytic blood films or blood absolute indices occurred in 12 cases, though only one patient became clinically anæmic. Ten patients developed some leukopenia but small dose reduction corrected this. In one patient, who already had hepatic cirrhosis following prolonged methotrexate therapy, thrombocytopenia required cessation of treatment. Biochemical hepatic function tests remained either normal or unchanged in all cases. There was no evidence of renal damage as judged by urine examination microscopy and blood urea estimations.

Liver biopsy results: Before treatment started 18 patients had a biopsy performed and all cases in whom therapy was fully established had biopsies at intervals of about 9 months during treatment.

The biopsy slides were examined by histopathologists (Dr P J Scheuer and Dr A Stansfeld) who classified the changes without prior knowledge of the patient or sequence of the biopsies. Seventeen different pathological features were assessed in each sample and the degree noted. The two pathological features which seemed of importance were cholestasis, present in 2 patients to minimal degree; and minimal portal enlargement and fibrosis without interference with lobular architecture, which was seen in 10 cases. This incidence of 10 out of 20 biopsied cases compares with 2 cases who had the portal fibrosis changes before azathioprine therapy. One of these was later unchanged and one became normal while therapy contined. One of the patients with post-treatment portal fibrosis also became normal later, giving 7 cases out of 20 in whom the minimal fibrosis might reasonably be attributed to azathioprine.

Azathioprine had been the only cytotoxic drug administered in 7 cases, of whom 2 had this minimal portal fibrosis; of these 2, one man had a high alcohol intake with raised transaminase and bilirubin before treatment, and the other had bouts of cardiac failure.

Discussion

Cytotoxic drugs have impressively altered the social outlook of many severe psoriatic patients. In some with erythroderma or those who required large doses of systemic corticosteroids to control their disease, these drugs have been lifesaving. It is in this perspective that the complications of cytotoxic drug therapy must be viewed.

Previous reports of hepatotoxicity with azathioprine have been complicated by the use of other drugs at the same time or before azathioprine. Corley *et al.* (1966) reported cholestasis and jaundice in a patient with autoimmune disease who had received prochlorperazine in addition to azathioprine. Zarday *et al.* (1972) demonstrated irreversible liver damage in a renal allograft patient who had been given cyclophosphamide, isoniazid and ethambutol in addition to azathioprine.

In the series of patients reported now, 12 out of 29 had received methotrexate (in more than a single dose) before azathioprine therapy. We are therefore dealing with a mixed group of patients and this must be considered in the assessment of results.

The lack of changes in biochemical liver function tests is reassuring, but the high incidence of portal fibrosis, even though of minimal severity and without evidence of any irreversible change, is worrying when the relatively short duration of treatment is considered. It seems mandatory for adequate monitoring by repeated liver biopsies to be undertaken if the drug is prescribed over a long period, so that the potential risk is evaluated.

Azathioprine is a useful drug in the management of severe psoriasis but its potential risk, especially to the liver, must be evaluated repeatedly in all cases.

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