METHOTREXATE* FOR PSORIASIS

A Preliminary Report

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THE efficacy of folic acid antagonists, which ushered in a new era in the treatment of psoriasis, was discovered fortuitously in 1951 when Gubner, August, and Ginsberg[1] noticed rapid clearing of psoriatic skin lesions in a patient with rheumatoid arthritis treated with Aminopterin.‡ Rees and associates[2, 3] reported on the extensive use of Aminopterin, and this became an accepted agent for treating selected cases of psoriasis. In 1958, Edmundson and Guy[4] reported on the oral use of Methotrexate* in cyclic dosages. Excellent results were later reported by other authors, with much fewer severe side effects than those occurring from the use of Aminopterin.

Mechanism of Action

Folic acid antagonists inhibit the enzyme, folic acid reductase, which catalyzes a necessary link in the metabolism of folic acid to tetrahydro-folic acid. The synthesis of purines, pyrimidines, and nucleic acids is subsequently dependent on this compound. Desoxyribonucleic acid (DNA) is one of the end products of folic acid metabolism; it is a vital component of all tissues, but especially of rapidly growing tissues such as the bone marrow, the gastrointestinal tract, and the skin. Van Scott and Reinertson[5] postulated that normal keratinization does not occur in persons who have psoriasis, because rapid epidermal reproduction takes place, precluding full maturation of the epidermal cells. Methotrexate stops mitosis, presumably by temporarily reducing the supply of DNA, and therefore allowing normal keratinization to occur in psoriatic skin.

Toxicity studies[6] have shown Methotrexate to be more effective and less toxic when given in large single doses at 7- to 10-day intervals than when given in small daily doses.

In experimental studies, the single parenteral dose LD50 for Methotrexate effective in dogs is 20 mg. per kilogram of body weight, whereas a single daily dose repeated for 15 consecutive days has an LD50 of 0.06 mg. per kilogram of body weight. Condit[7] studied a small group of patients having neoplasms who received intravenously a single dose of Methotrexate as large as 16 mg. per kilogram of body weight (a total of 1,000 mg.) without serious toxic effects.

**Methotrexate* (4-*amino*-n^{10}-*methyl*-*pteroylglutamic acid*), *Lederle Laboratories.*
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The drug is contraindicated during pregnancy or in patients with impaired hepatic or renal function. Methotrexate must be dispensed by a physician himself, not through his prescription filled by a pharmacist.

Method

We used the method reported by Van Scott, Auerbach, and Weinstein[8] in a few patients who had severe generalized psoriasis. We found the weekly parenteral administration of from 50 to 75 mg. of Methotrexate effective, but the inconvenience to the patient of making weekly trips to the office for the injections we believe greatly limits its acceptance by the patients.

The selection of patients was based on the following criteria: (1) the psoriasis had been resistant to previous treatment; (2) the patient was in good health; (3) the complete blood count, urinalysis, blood urea nitrogen, and hepatic function tests were normal; (4) the patient was not pregnant.

Methotrexate was given orally in a dosage of 25 mg. (ten 2.5-mg. tablets) at weekly intervals. All 10 tablets were consumed in one day, and the blood hemoglobin and white blood cell counts were repeated at weekly and later monthly intervals. Hepatic function studies were performed at one- to three-month intervals. The treatment program was based upon a suggestion by Dr. H. Lamar Callaway, of Duke University Hospital, Durham, North Carolina, to one of us (J. R. H.).

Results

Forty-five patients with adequate follow-up were evaluated. The average age was 46 years (range, from 14 to 76 years), and there were 31 males and 14 females in our study. The duration of therapy with Methotrexate averaged 15 weeks (range, from 4 to 27 weeks).

Results of therapy were evaluated by estimating the percentage of the total body covered by psoriasis before and after therapy. The "rule of nines" method was used for calculations (9 percent for head and each arm; 18 percent for anterior trunk, posterior trunk, and each leg). (*Table 1.*)

Comment

Psoriasis vulgaris is a disease with an unpredictable course and there may be improvement with or without therapy. Therefore, it is difficult to conduct a controlled study on therapy for psoriasis.

This is a preliminary report on results in 45 selected cases of psoriasis vulgaris treated with Methotrexate given orally at seven-day intervals.

Many of our patients received concomitant therapy in the form of hospitalization, Goeckerman routine, and topically applied corticosteroids with plastic occlusive dressings. The average percentage of the total body covered by psoriasis

Table 1.—*Summary of data from 45 patients with psoriasis treated with Methotrexate*

Percentage of total body covered by psoriasis	
Before Methotrexate	Average—72
	Range—25 to 100
After Methotrexate	Average—4
	Range—0 to 25 (3 cases greater than 10)
	Complete clearing—0 (21 cases)
Abnormal laboratory studies *after* Methotrexate	
White blood cell count	0
Blood hemoglobin	0
Platelets	0
Liver function	
Sulfobromophthalein (34 cases)	8 (highest 9%)
Alkaline phosphatase (12 cases)	0
Transaminase (16 cases)	0
Other (10 cases)	1
Blood urea nitrogen	0
Urinalysis	0
Side effects, 15 (33⅓%) of 45 cases	
Nausea	9 (19%)
Headache	4 (8%)
"Burning" of skin lesion	3 (6%)
Herpes zoster	1 (2%)
Convulsion	1 (2%)

was 72 percent before therapy and only 4 percent after therapy. The more significant point is that 21 patients had complete clearing.

This is a small series of patients and a relatively short follow-up period (average 15 weeks). We plan to follow up these patients over the next several years and to increase the number of patients under treatment. We are concerned about possible rebound phenomenon as experienced with steroids taken orally for psoriasis.

No significant abnormalities in the white blood cell count, hemoglobin, platelets, blood urea, or urinalysis occurred in our patients. There were a few minimal changes in hepatic function studies in eight patients. O'Rourke and Eckert[9] and

others[10, 11] have reported hepatic damage in psoriatic patients who were treated with Methotrexate. Although Black and associates[10] noted that of 21 psoriatic patients only three had transient elevations of serum glutamic oxaloacetic transaminase levels, Ryan's group[11] found evidence of some impairment of the liver in all 14 patients treated with Methotrexate. Although our study revealed no significant hepatic damage with weekly oral doses, future follow-up study will be valuable in determining the long-term effect of the drug on hepatic function.

Side effects occurred in one third of our patients, but were easily controlled. The nausea was eliminated by antacid tablets, or by taking five Methotrexate tablets on each of two successive days each week (2 of 45 patients) rather than 10 tablets in one day each week.

Methotrexate is a potent drug and should not be dispensed haphazardly. Patients must have psoriasis that is not controlled by other proved methods of therapy. The drug should never be administered to patients with hepatic or renal disease.

Two of the 45 patients died, but medical problems other than Methotrexate toxicity were responsible for their deaths. The first patient had coronary insufficiency and death followed a second acute myocardial infarction. The second patient died as the result of septicemia and systemic infection with *Candida albicans*. Hematologic abnormalities, which have been described in reports of deaths from toxic effects of Methotrexate,[10] were not a problem in either of these cases.

Our preliminary data show that weekly oral administration of Methotrexate is an excellent method of controlling severe psoriasis. The drug is easy to administer and obviates weekly trips to the physician's office for injection of the medication. It has good acceptance by patients.

Summary

A preliminary study of 45 patients with severe psoriasis vulgaris treated orally with Methotrexate is presented. We believe that Methotrexate tablets given orally in weekly single doses of 25 mg. is an effective method of treating selected cases of psoriasis vulgaris.

References

1. Gubner, R.; August, S., and Ginsberg, V.: Therapeutic suppression of tissue reactivity; effect of Aminopterin in rheumatoid arthritis and psoriasis. Am. J. M. Sc. **221**: 176-182, 1951.
2. Rees, R B.; Bennett, J. H., and Bostick, W. L.: Aminopterin for psoriasis. A.M.A. Arch. Dermat. **72**: 133-143, 1955.
3. Rees, R. B., and Bennett, J. H.: Further observations on Aminopterin for psoriasis. J. Invest. Dermat. **32**: 61-66, 1959.
4. Edmundson, W. F., and Guy, W. B.: Treatment of psoriasis with folic acid antagonist. A.M.A. Arch. Dermat. **78**: 200-203, 1958.

5. Van Scott, E. J., and Reinertson, R. P.: Morphologic and physiologic effects of chemotherapeutic agents in psoriasis. J. Invest. Dermat. **33:** 357-369, 1959.

6. Berlin, N. I. (moderator); Rall, D.; Mead, J. A. R.; Freirich, E. J.; Van Scott, E. J.; Hertz, R., and Lippsett, M. B.: Folic acid antagonists; effects on cell and patient. Ann. Int. Med. **59:** 931-956, 1963.

7. Condit, P. T.: Studies of folic acid vitamins. II. Acute toxicity of Aminopterin in man. Cancer **13:** 222-228, 1960.

8. Van Scott, E. J.; Auerbach, R., and Weinstein, G. D.: Parenteral Methotrexate in psoriasis. Arch. Dermat. **89:** 550-556, 1964.

9. O'Rourke, R. A., and Eckert, G. E.: Methotrexate-induced hepatic injury in adult. Case report. Arch. Int. Med. **113:** 191-194, 1964.

10. Black, R. L.; O'Brien, W. M.; Van Scott, E. J.; Auerbach, R.; Eisen, A. Z., and Bunim, J. J.: Methotrexate therapy in psoriatic arthritis; double-blind study on 21 patients. J.A.M.A. **189:** 743-747, 1964.

11. Ryan, T. J.; Vickers, H. R.; Salem, S. N.; Callender, S. T., and Badenoch, J.: Treatment of psoriasis with folic acid antagonists. Brit. J. Dermat. **76:** 555-564, 1964.

12. Rees, R. B.; Bennett, J. H.; Hamlin, E. M., and Maibach, H. I.: Aminopterin for psoriasis; decade's observation. Arch. Dermat. **90:** 544-552, 1964.