Textbook of Rheumatology

Fourth Edition Volume 1

WILLIAM N. KELLEY, M.D.
Chief Executive Officer
University of Pennsylvania Medical Center
Executive Vice President and Robert G. Dunlop
Professor of Medicine and Biochemistry and Biophysics
University of Pennsylvania
Dean, University of Pennsylvania School of Medicine
Philadelphia, Pennsylvania

EDWARD D. HARRIS, Jr., M.D.
Arthur L. Bloomfield Professor and Chairman
Department of Medicine
Stanford University School of Medicine
Stanford, California

SHAUN RUDDY, M.D.
Elam Toone Professor of Internal Medicine,
Immunology, and Microbiology
Chairman
Division of Rheumatology, Allergy, and Immunology
Department of Internal Medicine
Medical College of Virginia
Virginia Commonwealth University
Richmond, Virginia

CLEMENT B. SLEDGE, M.D.
John B. and Buckminster Brown Professor of Orthopedic Surgery
Harvard Medical School
Chairman
Department of Orthopedic Surgery
Brigham and Women's Hospital
Boston, Massachusetts

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.
Philadelphia London Toronto Montreal Sydney Tokyo

W.B. SAUNDERS COMPANY
Harcourt Brace Jovanovich, Inc.

The Curtis Center
Independence Square West
Philadelphia, Pennsylvania 19106

Library of Congress Cataloging-in-Publication Data

Textbook of rheumatology / William N. Kelley . . . [et al.].—
4th ed.

p. cm.

Includes bibliographical references and indexes.

ISBN 0-7216-3157-6 (set)

1. Rheumatology. I. Kelley, William N., 1939–
[DNLM: 1. Arthritis. 2. Rheumatic Diseases.
WE 544 T355 1993]

RC927.T49 1993 616.7'23—dc20

DNLM/DLC
for Library of Congress 92-48331
CIP

TEXTBOOK OF RHEUMATOLOGY, Fourth Edition ISBN

Volume I 0-7216-3155-X
Volume II 0-7216-3156-8
Two Volume Set 0-7216-3157-6

Printed in the United States of America.

Last digit is the print number: 9 8 7 6 5 4 3 2 1

Chapter 47

Methotrexate

Michael E. Weinblatt

Methotrexate has become an established treatment for rheumatoid arthritis. Low-dose weekly methotrexate was approved by the United States Food and Drug Administration in 1988 as a therapy for active rheumatoid arthritis. There is also significant interest in low-dose methotrexate as a therapy for a variety of other autoimmune, inflammatory, and rheumatologic conditions.

CHEMICAL STRUCTURE

Methotrexate is an antimetabolite and is a structural analogue of folic acid. The structure of folic acid (pteroylglutamic acid) consists of three elements: a multiring pteridine group linked to a para-aminobenzoic acid that is connected to a terminal glutamic acid residue (Fig. 47–1). Methotrexate differs from folic acid in that an amino group substitutes for a hydroxyl group in position 4 of the pteridine portion of the molecule and by the addition of a methyl group in position 10 of the 4 amino–benzoic acid structure (see Fig. 47–1).

BIOCHEMICAL PHARMACOLOGY

Dietary folic acid is reduced enzymatically by the enzyme dihydrofolate reductase to both dihydrofolate and tetrahydrofolate, which are metabolically active reduced folates. These reduced folates are essential in the conversion of homocysteine to methionine, in the metabolism of histidine, in the synthesis of purines, and in the biosynthesis of thymidylate, which is required for DNA synthesis. Methotrexate, an antimetabolite, binds and inactivates the enzyme dihydrofolate reductase, resulting in the depletion of metabolically active intracellular folates with subsequent inhibition of the synthesis of thymidylate and inosinic acid (Fig. 47–2). Additionally, methotrexate affects protein synthesis by preventing the conversion of glycine to serine and homocysteine to methionine. Methotrexate exerts its maximum inhibitory effect on cells that are actively undergoing DNA synthesis, particularly those cells in the S phase of the cell cycle. Cells undergoing rapid cellular turnover such as in the epidermis and gastrointestinal tract are the most susceptible to the effects of the drug. Folinic acid (leucovorin), a fully reduced metabolically active folate coenzyme, functions without the need for reduction by the enzyme dihydrofolate reductase. Folinic acid (leucovorin) is used to "rescue" normal cells from the toxicity induced by methotrexate. Folinic acid is used as a "rescue" agent in cancer chemotherapy and as a treatment for acute methotrexate overdose and hematologic toxicity.

Folates in the blood have a single terminal glutamate structure. Most intracellular folates are metabolized to a polyglutamated compound. These polyglutamates have longer cellular retention and are more efficient cofactors than the monoglutamate compound. Similar to the folate cofactors, methotrexate also is metabolized from a monoglutamate to a polyglutamated derivative. Methotrexate polyglutamates have stronger cellular retention, remain within the cell in the absence of extracellular drugs, and are more potent than the monoglutamate structure.[1] The synthesis of the methotrexate polyglutamates increases with the duration of therapy. The polyglutamated derivatives predominate in hepatic tissue, which may be a factor in toxicity. The concentration of hepatic methotrexate polyglutamates decreases after folinic acid therapy.[2]

The mechanism of action of low-dose methotrexate in rheumatoid arthritis is not known. Whether its therapeutic effect is due to its antifolate activity, immunomodulating properties, immunosuppressive properties, or anti-inflammatory effects is under study. It is most likely that a combination of these factors accounts for its therapeutic profile in rheumatoid arthritis. High-dose methotrexate at doses used for cancer therapy has immunosuppressive properties including suppression of antibody formation and suppression of primary and secondary immune response.[3] In rheumatoid arthritis, however, a profound immunosuppressive effect has not been documented with low-dose methotrexate. Neither a global suppression of T cell function nor changes in T cell subsets were reported in short-term studies in rheumatoid arthritis.[4, 5] After 2 years of therapy, however, a significant increase in the percentage of T3 and T4 cells and an increase in thymidine incorporation responses to selected mitogens and antigens were noted.[6] These changes may have reflected the reduction in prednisone dose and overall improvement in disease activity that occurred after 2 years of drug administration rather than a selective effect of the drug.

The effect of methotrexate on in vivo gamma M immunoglobulin (IgM) rheumatoid factor production

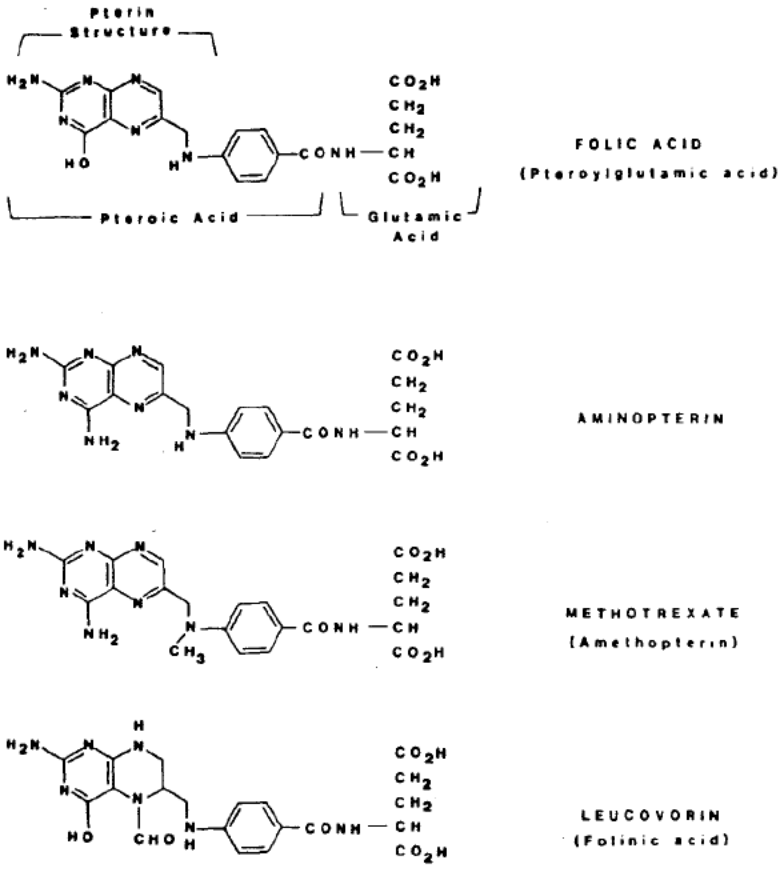

Figure 47–1. Structure of folic acid, aminopterin, methotrexate, and leucovorin.

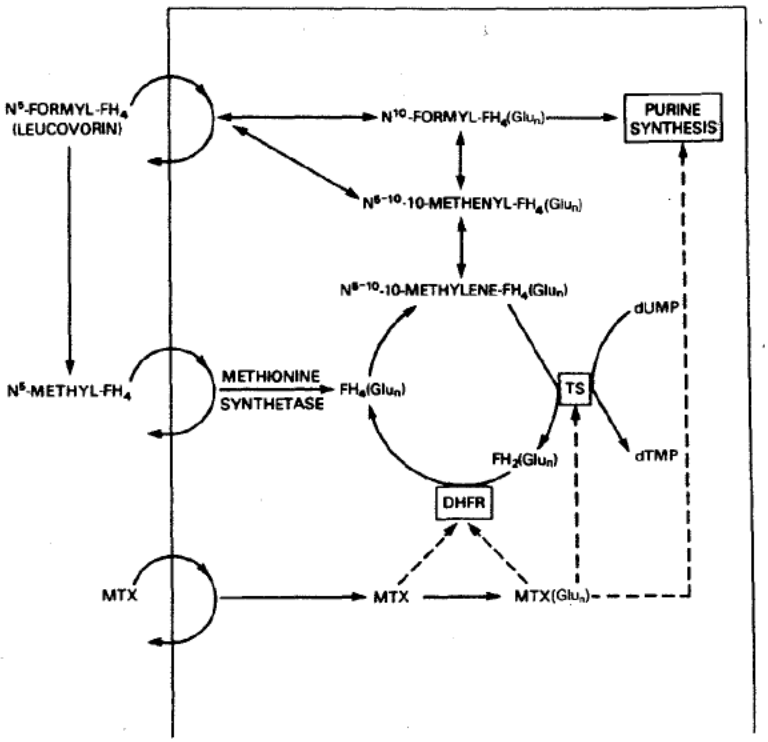

Figure 47–2. Mechanism of action of methotrexate. MTX, Methotrexate; DHFR, dihydrofolate reductase; TS, thymidylate synthetase; FH_4, tertrahydrofolate; FH_2, dihydrofolate; Glu, glutamyl; dTMP, thymidylate; dUMP, dioxyuridylate. Broken lines indicate enzyme inhibition. (From Jolivet, J., Cowan, K. H., Curt, G. A., Clendeninn, N. J., and Chabner, B. A.: The pharmacology and clinical use of methotrexate. N. Engl. J. Med. 309:1095, 1983. Reprinted by permission of the New England Journal of Medicine.)

as measured by agglutination assays has been variable.[4, 5, 7] A suppression of IgA rheumatoid factor and IgM rheumatoid factor as measured by an enzyme-linked immunosorbent assay (ELISA), however, was observed in vivo in patients enrolled in multicenter trials of methotrexate.[8] A suppression of in vitro rheumatoid factor production has also been observed.[9] Inhibition of selected interleukin-1 (IL-1) activity has been reported in vitro, but the in vivo data are inconclusive.[10] Methotrexate exerts an antiproliferative effect on peripheral blood mononuclear cells in vitro,[11] inhibits in vitro vascular epithelial cell proliferation and in vivo neovascularization, and may affect adenosine release.[12, 12a]

An anti-inflammatory effect with methotrexate has been suggested by its rapid onset of action and the flare after drug discontinuation. In an air sac model of inflammation, pretreatment of mice with low-dose methotrexate inhibited neutrophil migration that was induced by both C5a and leukotriene B_4.[13] In vivo chemotaxis after stimulation with C5a and leukotriene B_4 was blocked in psoriasis patients after methotrexate administration.[14, 15] Suppression of leukotriene B_4 ex vivo was observed with methotrexate in rheumatoid arthritis patients.[16]

Low-dose methotrexate inhibited adjuvant induced and streptococcal cell wall induced arthritis.[17] In adjuvant arthritis, methotrexate inhibited macrophage activation, inhibited neutrophil migration, and prevented the induction of an IL-2 deficiency in animals.[17]

PHARMACOKINETICS

Methotrexate at low doses can be administered by either an oral or parenteral route. The bioavailability of low-dose oral methotrexate is relatively high, but there is individual patient variability. In 41 rheumatoid patients who received 10 mg per m^2 of oral methotrexate, a mean bioavailability of 0.7 with a range of 0.4 to 1.0 was reported.[18] Patients not responding on oral methotrexate should be given a trial of parenteral methotrexate to ensure complete bioavailability. Intramuscular and subcutaneous methotrexate are rapidly absorbed; the maximum serum concentration is attained within 2 hours of injection. The pharmacokinetics of subcutaneous methotrexate is the same as intramuscular methotrexate in rheumatoid arthritis.[19] Methotrexate diffuses into synovial fluid at concentrations equal to serum levels.[18]

Methotrexate distributes throughout the body, with higher concentrations found in intestinal epithelium and hepatic cells. Methotrexate is only 50 to 60 percent bound to plasma proteins. An increase in free methotrexate owing to its displacement from albumin by more highly protein bound drugs such as aspirin, nonsteroidal anti-inflammatory drugs, and sulfonamides can occur. This displacement appears to be of limited clinical significance with low methotrexate doses because the increase in free methotrexate may only be modest. Methotrexate may undergo hepatic metabolism by the enzyme aldehyde oxidase to 7-hydroxymethotrexate. Excretion of methotrexate and its metabolites is by the kidney by both glomerular filtration and proximal tubular secretion. Organic acids such as phenylbutazone, penicillin, sulfonamides, salicylates, and probenecid competitively inhibit tubular secretion, which may affect methotrexate clearance. The plasma half-life of methotrexate is less than 10 hours but increases in the presence of renal insufficiency. The toxic effect of methotrexate on normal tissue is generally related to the duration of exposure rather than the peak level of the drug.

Several kinetic studies have failed to note a significant interaction between low-dose methotrexate and a variety of nonsteroidal anti-inflammatory drugs.[20, 21] With high doses of methotrexate, coadministration of nonsteroidal anti-inflammatory drugs or aspirin may be toxic and must be avoided. Drugs that affect renal function, such as probenecid, or drugs with antifolate activity, such as trimethoprim/sulfamethoxazole, should be used with great caution owing to an increased risk for toxicity.

RHEUMATOID ARTHRITIS

Because aminopterin was a potent inhibitor of connective tissue proliferation, Gubner et al.[22] in 1951 administered this drug to six patients with rheumatoid arthritis. A rapid improvement in the arthritis symptoms occurred in five of the six patients, but exacerbations followed drug discontinuation. In 1972, Hoffmeister[23] reported the beneficial effect of low-dose intramuscular methotrexate in 29 patients. Hoffmeister expanded his series to include 78 patients with a treatment follow-up as long as 15 years.[24] Forty-five patients (58 percent) had a "marked" improvement, including 28 patients who were judged to be in "complete remission." Seven patients discontinued therapy owing to adverse reactions, including elevation in liver blood tests, stomatitis, headaches, nausea, or increasing fatigue.

In another open study, 67 patients received low-dose oral weekly methotrexate for a treatment period that ranged from 3 months to 10 years.[25] A "one-step" response was noted in 33 (49 percent) and a "two-step" response was noted in 18 (27 percent) of the patients. Thirty-four patients discontinued therapy, including 11 because of nausea or gastrointestinal intolerance.

There was significant improvement in a 21-patient open study of 38 weeks' duration. The methotrexate dose ranged from 7.5 to 25.0 mg per week.[26] Eleven (52 percent) of the patients had an "unequivocal" response, five (24 percent) had an "equivocal" response, and two patients were unresponsive to therapy. Three patients discontinued methotrexate: two because of noncompliance and fear of toxicity

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.