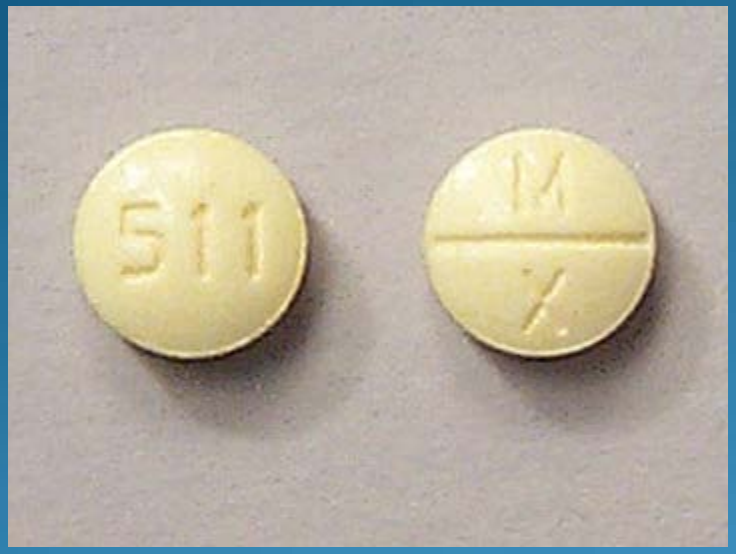
Methotrexate

Methotrexate

- In the 1950's, MTX (Amethopterin) was found to be effective against Psoriasis.

- 20 years later MTX received an FDA indication for Psoriasis, followed by Rheumatoid Arthritis in the late 1980's

Methotrexate

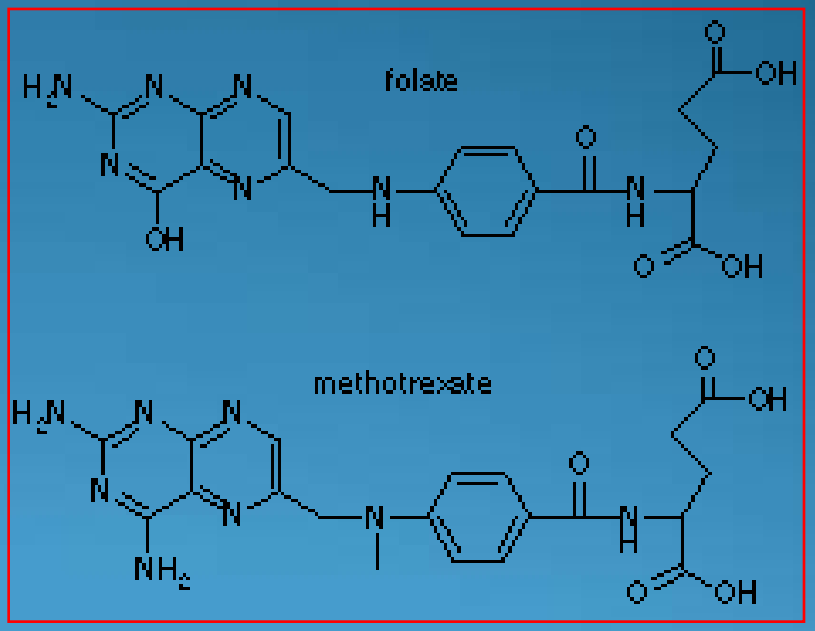


- **Class**
  - Antimetabolite, Antirheumatic, Cytotoxic
- **How supplied**
  - Oral tablet (scored): 2.5, 5, 7.5, 10, 15mg
  - Can also be given IM, IV, or Intrathecal
- **FDA labeled indications in Dermatology**
  - Psoriasis
  - Sezary Syndrome

Chemical Structure

- 4-amino-N_{10}methyl pteroglyglutamic acid, a weak organic acid

- Similar in structure to folic acid, the natural substrate for the enzyme dihydrofolate reductase



Pharmacokinetics

- **Bioavailability**
  - Rapidly absorbed through the GI tract with peak levels occurring 1 hour after ingestion (more rapid for IV/IM)
  - PO route preferred because it provides more reliable blood concentrations than IV
    - Can be incomplete and variable with higher doses
    - Decreased with food intake (dairy) in children, but not in adults
    - Non-absorbable Abx (Neomycin) can significantly reduce absorption.

Pharmacokinetics

- **Distribution**
  - Well distributed throughout the body except the brain due to poor penetration of the blood-brain barrier

Pharmacokinetics

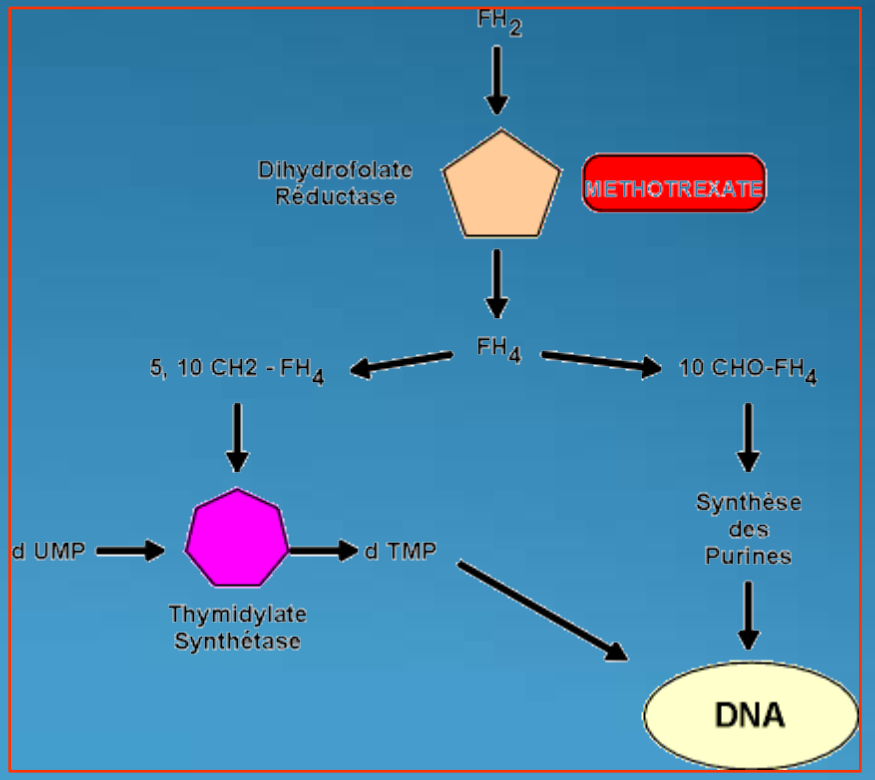
- **Metabolism/Excretion-** Triphasic Reduction
  - Phase 1-Distribution of the drug throughout the body-(45 minutes)
  - Phase 2-Renal excretion-primary means of excretion*; (2-4 hours)
  - Phase 3-Terminal $t_{1/2}$- reflects slow release of MTX by its target substrate in the tissue; (10- 27 hours)

Pharmacokinetics

- 50% of MTX is bound to plasma proteins at any one time
  - Unbound form of drug is the active form
  - Drugs that increase the free fraction: sulfonamides, salicylates, tetracyclines, chloramphenicol, sulfonylureas, retinoids, barbiturates, probenecid, & phenytoin
- MTX is actively transported into cells and metabolized intracellularly. These metabolites are also potent inhibitors of dihydrofolate reductase.

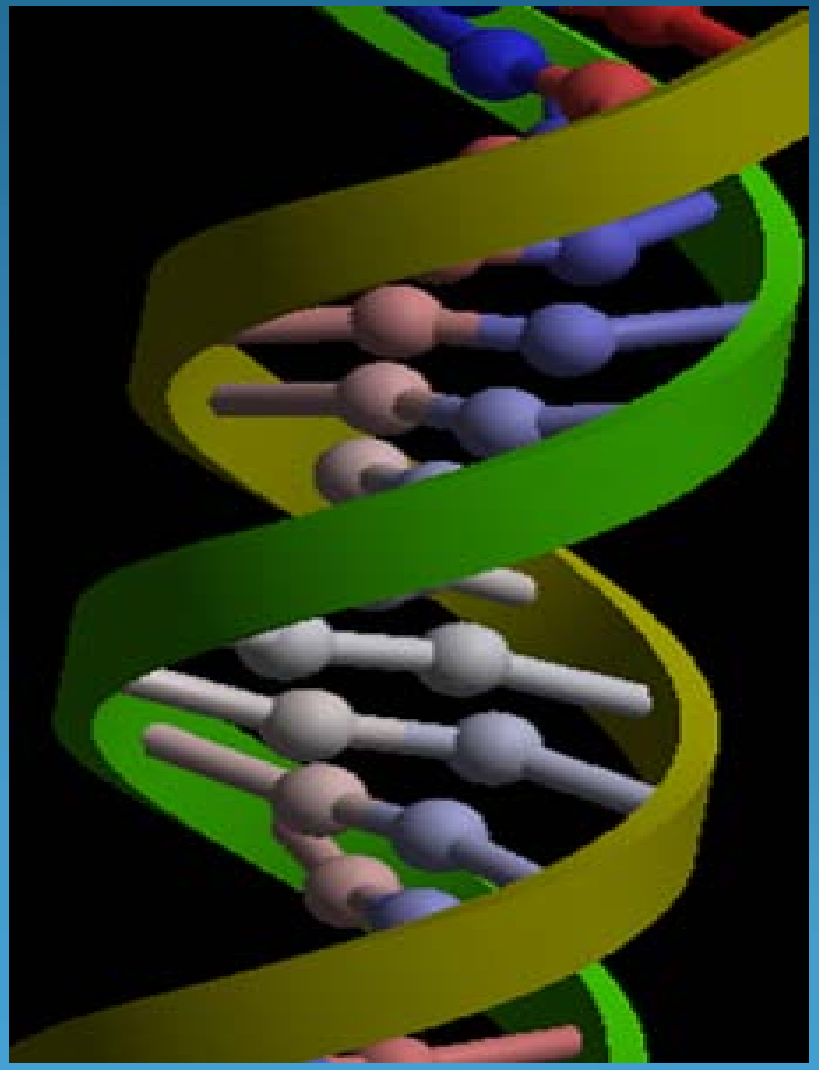
Pharmacodynamics

- MTX competitively and irreversibly binds to dihydrofolate reductase
- MTX competitively but reversibly binds to thymidylate synthetase

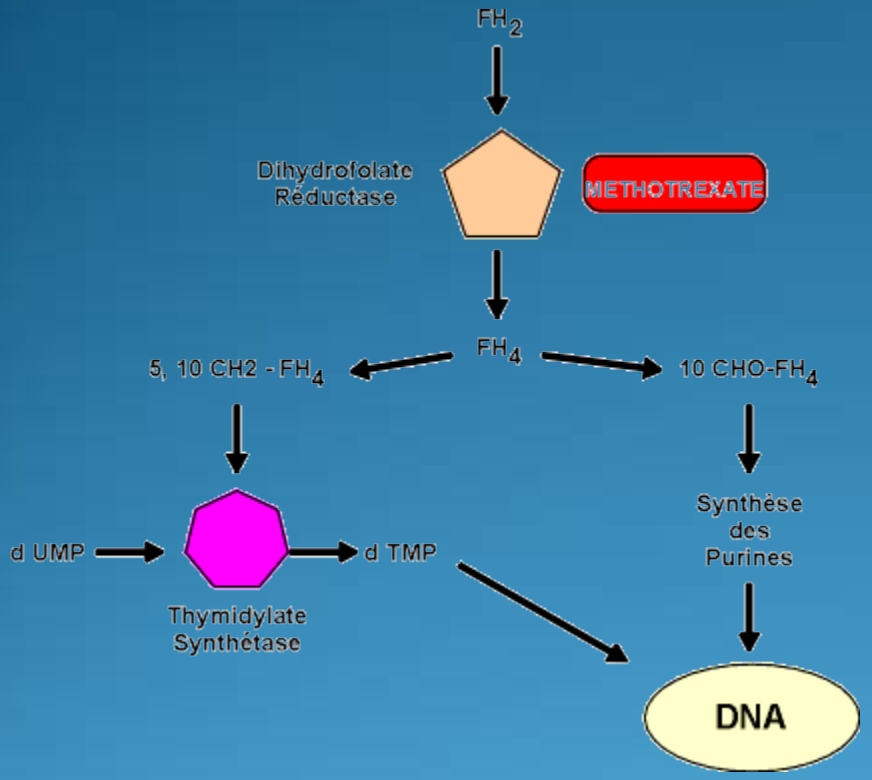


Pharmacokinetics

- Depletes Tetrahydrofolate, a building block of thymidylate and purine nucleotides used in DNA/ RNA synthesis
- Inhibitor of cell division, *S-phase of cell cycle



Pharmacokinetics



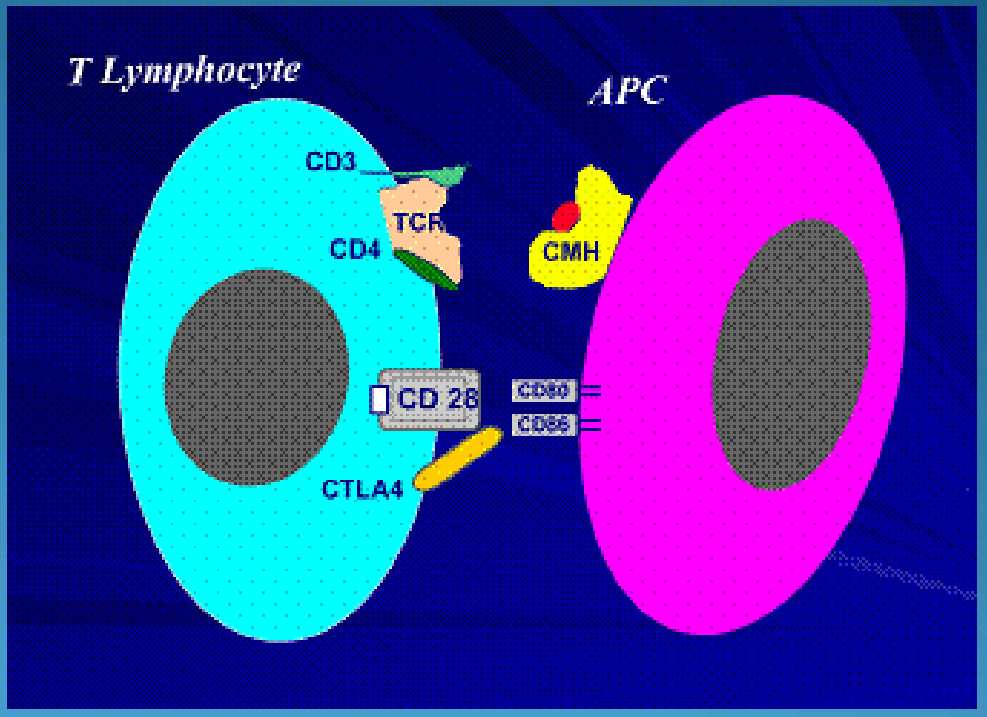
- MOA can be inhibited by Leucovorin or thymidine (used for acute hematological toxicity)
- **Leucovorin** (folinic acid, citrovorum factor)-folate coenzyme that bypassed the reaction catalyzed by Dihydrofolate reductase
- **Thymidine** is converted to thymidylate bypassing the reaction catalyzed by thymidylate synthetase.

Pharmacokinetics

- Other mechanisms of action:
  - (-)'s AICAR transformylase: Inc. Adenosine in tissues (Anti-inflammatory effect)
  - (-)'s Methionine Synthetase: Dec. S-adenylmethionine (Proinflammatory effect)
- *Explains the paradox of using folic acid during MTX therapy

Mechanism in Psoriasis

- Inhibits DNA synthesis in immunologically competent cells thereby suppressing primary and secondary antibody responses.



Clinical Use

- FDA approved for Dermatology
  - Psoriasis, Sezary
- Contraindications
  - Absolute-pregnancy, lactation (Category X)
  - Relative-Unreliable patient, CRI, DM, Obesity, Hepatic Disease, Hematological abnormalities, Male or female contemplating pregnancy, active infectious disease or history of potentially serious infection that could reactivate, immunodeficiency

Indications for MTX in Psoriasis

- Erythrodermic Psoriasis
- Psoriatic Arthritis
- Pustular form; generalized or localized debilitating form
- Debilitating disease
- Extensive, severe plaque psoriasis failing conventional tx(>20 % surface involvement)
- Lack of response to Phototx or systemic retinoids

Clinical Course

- 75-80% of patients with Psoriasis will respond to MTX therapy
- An initial response is typically seen within 1-4 weeks
- A complete response usually occurs in 2-3 months

Dosing

- Oral weekly doses
  - Single weekly dose or 3 divided doses/24 hours
- Weekly IM
  - Useful in patients with poor compliance or associated nausea
- Once weekly dosing significantly reduces the risk of heme abnormalities

Dosing

- Test dose of 5-10 mg followed a lab draw in 7 days (CBC/LFT)
- Gradually increase dose by 2.5-5 mg q week (IM/IV doses can be much higher due to rapid renal clearance)
- Normal target dose: 10-15 mg /week, rarely exceeding 30 mg /week.
- When max benefit is achieved clinically, dec. dose gradually to maintain (with IM, inc. dosing interval

GI -Adverse Effects

- Nausea/anorexia (common), Vomiting/diarrhea/ulcerative stomatitis (less common)
- Hepatoxicity (Long term use)
  - Liver fibrosis/cirrhosis(? Incidence):
  - Low risk: cumulative dose <1.5 gram
  - High risk: cumulative dose >4 gm

GI Adverse Effects

- Clinical course of hepatic fibrosis non aggressive; may not progress despite continued tx or may reverse when tx is discontinued

Pulmonary-Adverse Effects

- Acute Pneumonitis -can occur with small dose; idiosyncratic and severe resulting in death if MTX is not stopped
- Pulmonary Fibrosis (inc. assoc. with RA -5%)
  - Infrequent in Psoriasis
  - CXR/ PFT's are unreliable, therefore CXR should only be done if patient is symptomatic

Hematological Adverse Effects

- Pancytopenia -*Most life threatening side effect
  - Risk factors: Drug interactions, renal disease, elderly patients, no folate supplementation, daily MTX dosing, 1st 4-6 weeks of therapy, Albumin <3, major illnesses
- Macrocytic indices without anemia are more common at dermatological doses

Malignancy Risk

- Rarely reported
  - EBV has been linked to these few cases and many demonstrated regression of the lymphoma with cessation of MTX.
- No evidence exists that MTX increases the risk of subsequent malignancies in patients with psoriasis

Reproductive Effects

- Women
  - No inc. risk of fetal abnormalities in subsequent pregnancies.
  - Teratogenicity risk is small, but still important to avoid fetal exposure.
  - Reliable birth control is needed during tx
- Men
  - Should avoid impregnating while on tx
  - Can experience reversible oligospermia

Renal Adverse Effects

- Precipitation of drug in renal tubules-only occurs at very high doses (chemotherapy doses)

Other Adverse Effects

- Mild alopecia, headaches, fatigue, dizziness, potential photo toxicity (Locus minoris)
- Rare-anaphylaxis, acral erythema, epidermal necrosis, vasculitis, osteopathy
- Erosion of psoriatic plaques (Pearce and Wilson)

Drug Interactions

- Drugs that inc. MTX levels
  - salicyates, NSAIDs, sulfonamides, dipyridamole, probenecid, phenothiazines, phenytoin, tetracyclines
- Drugs that also inhibit folate metabolic pathway
  - trimethoprim, sulfonamides, dapsone
- Drugs that are synergistically hepatotoxic
  - systemic retinoids, alcohol

Monitoring

- Baseline labs-
  - CBC, LFT, hepatitis serologies, Chemistry (Renal fxn), PPD and HIV test for patients at risk; in elderly determine CrCl (www.medcalc.com)

Monitoring

- Follow up labs
  - CBC (WBC count <3500 or platelets <100K), LFT's (AST/ALT >2x baseline), and Chemistry
  - Repeat weekly for 2-4 weeks and then gradually decrease frequency to 3-4 months long term
  - Repeat 5- 6 days after dose escalations
  - Increase frequency if dose is escalated, new medications are added, or patient becomes ill

Monitoring-Liver Biopsy

- Diagnostic test for MTX induced Hepatic fibrosis and cirrhosis
- Current Dermatology Guidelines
  - Biopsy after 1-1.5 gm cumulative dose
- “Delayed Baseline” Liver Biopsy 3-6 months after MTX tx for low risk patients
- True Baseline Liver Biopsy for high risk patients
  - personal or family hx of liver disease, exposure to known hepatotoxins, hx of EtOH or IVDA, DM, obesity and abnormal baseline LFT’s.

Monitoring-Liver Biopsy

- Repeat Biopsies
  - After every 1.5-2.0 gm total dose for low risk patient
  - After every 1.0 gm total dose for higher risk patients
  - Every 6 months for patients with grade IIIA (mild fibrosis) liver biopsy changes

Alternatives to Biopsy

- Zachariae suggests using 3 screening modalities to decrease the number of liver biopsies done.
  - Liver ultrasound
  - Radionuclide scans/ aminopyrine breath test
  - PIIINP (amino terminus of type III procollagen peptide)- marker of organ fibrosis

MTX Prices

- **Walmart**
  - $24.36 for 30 tabs= $0.81/tab
- **UVA**
  - $24.70 for 30 tabs= $0.82/tab
- **CVS**
  - $54.59 for 30 tabs= $1.82/tab