CHAPTER 26

METHOTREXATE USES IN DERMATOLOGY

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STRUCTURAL FEATURES

Dihydrofolate reductase (DHFR) is an enzyme that catalyzes the conversion of dihydrofolate to tetrahydrofolate; it is an essential cofactor in the synthesis of thymidylate and purine nucleotides, and therefore DNA/RNA. Methotrexate (MTX) (4-amino-N10-methyl-pteroylglutamic acid) inhibits DHFR competetively. Pteroylglutamic acid is structurally a synthetic analogue of folic acid, which is a natural substrate for this enzyme. MTX also partially inhibits (reversibly) thymidylate synthase and suppresses cell division in the S phase.[1] By inhibiting DNA synthesis, MTX limits epithelial hyperplasia, reinforces the apoptosis of activated T cells, and inhibits the chemotaxis of neutrophils.[2] In addition, the drug is responsible for decreasing the synthesis of a range of proinflammatory cytokines such as tumor necrosis factor α (TNF-α) and interleukin-1 (IL-1).[3]

Absorption And Dispersion Of Mtx

The pharmacokinetic characteristics of MTX depend on the route of administration.[3] It can be administered through oral, intravenous, intramuscular, or subcutaneous routes.

One hour after oral administration, the distribution in the body and active cellular uptake are complete. Time to reach peak levels after oral administration is slower than other administration routes. Oral absorption of MTX of doses above 15 mg may not be fully achieved; only parenteral administration can reach blood more safely (4,5). Evidence that MTX absorption is affected by food is contradictory.[3,5-7]

Especially in children, the bioavailability of the drug may be reduced when taken together with food, especially dairy products; however, in adults, this is not the case. Also, antibiotics such as neomycin, which is not absorbed from the gastrointestinal tract, significantly reduce the absorption of MTX. Although MTX largely distributes in the whole body, it cannot reach the brain since it does not cross the blood-brain barrier easily.[1]

There is no difference in bioavailability of MTX between subcutaneous or intramuscular injection. Therefore, taking into consideration pain at the intramuscular injection site, there are no arguments in favor of selecting this route. After injection, MTX is absorbed immediately and completely, achieving higher blood serum concentrations.[3]

After intramuscular injection, peak concentrations are achieved in 30 to 60 minutes. At serum concentrations of MTX exceeding 100 μM, the drug undergoes passive intracellular diffusion.[5]

Metabolism And Excretion

When MTX is absorbed, the plasma level decreases are triphasic. The first phase occurs rapidly (0.75 hours), and in this period, the drug is distributed throughout the whole body. The second phase of decreased plasma levels is the period of renal excretion, which lasts 2-4 hours. MTX is a weak organic acid, and is usually excreted by the kidneys. Therefore, glomerular filtration and tubular secretion are responsible for interactions with other drugs such as weak acids like active salicylates, probenecid, and sulphonamides. The third phase is a terminal half-life and lasts 10 to 27 hours. This phase primary reflects the slow release of the portion of the drug connected to the DHFR from the tissue. Approximately 50% of the MTX is bound to plasma proteins during circulation. The active portion is the fraction that freely diffuses in plasma. Therefore, any drug that can increase the amount of free MTX (such as sulfonamide and salicylates) can also increase the potential toxicity as well as being able to increase the beneficial effects on the tissue. MTX enters cells not by diffusion but by active transport.[1,5]

Mechanism of action

Methotrexate is a folate antagonist that was originally conceived as an anti-malignancy drug. Its primary metabolite, polyglutamate, competitively inhibits dihyrofolate reductase, preventing the reduction of folate cofactors. Pyrimidine synthesis is prevented by inhibition of thymidylate synthesis. Other folate-dependent enzymes inhibited by polyglutamate include aminoimidazole-carboxamide-ribonucleoside (AICAR) transformylase. The inhibition of AICAR impairs purine synthesis. The methylation of homocysteine to methionine is also inhibited, thereby affecting the synthesis of polyamines such as spermidine and spermine. The

TABLE. Drugs that increase the toxicity of MTX

Mechanism	Drug
Reduction in renal elimination of MTX	Nephrotoxins Salicylates Nonsteroidal anti-inflammatory drugs
Increase in the toxic effects of methotrexate drugs	Trimethoprim - sulfametoxazol Ethanol Fenilbutazon
Reduction in tubular secretion	Salicylates Sulfonamides Cephalothin Penicillin Colchicine
Prevention of bonding of MTX to plasma proteins	Salicylate Probenisid Barbiturat Phenytoin
Increase in MTX intracellular accumulation	Probenecid dipyridamole
Hepatotoxicity	Retinoid

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