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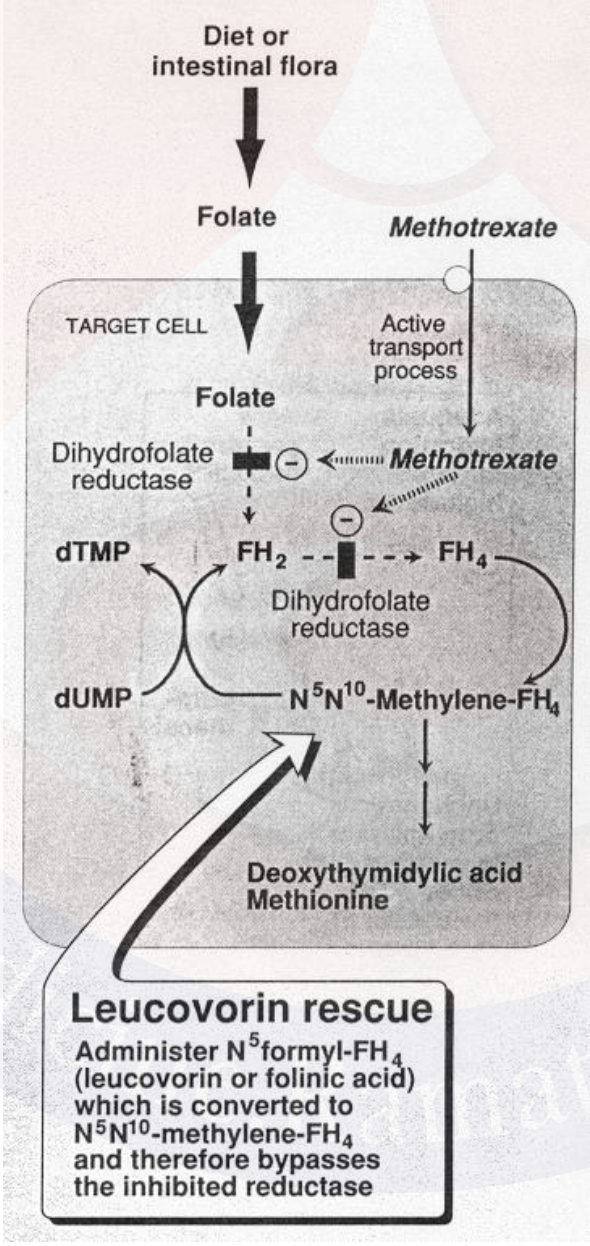
Leucovorin (Folinic acid)

LECOVORIN is the formyl derivative and active form of FOLIC ACID.

LECOVORIN is preferentially taken up by normal cells and bypasses the blocked enzyme & replenishes the folate pool.



LEUCOVORIN

GENERAL INFORMATION

LEUCOVORIN decreases the hematopoietic toxicity by supplying the necessary tetrahydrofolate co-factor, the synthesis of which is blocked by methotrexate.

Intravenous leucovorin should be administered as promptly as possible for the treatment of accidental overdosages of folic acid antagonists. Efficacy depends on early administration, the drug should be given within 1 hour of poisoning if possible. The effective of leucovorin in counteracting toxicity decreased with increase in time between folic acid antagonist administration and leucovolin rescue; usually ineffective if administered after a delay of 24 hours.

DO NOT administer leucovorin intrathecally even to treat accidental overdosage of intrathecally administered folic acid antagonists

INDICATION

To counteract the hematologic toxicity of folic acid antagonist such as methotrexate, trimethoprim and pyrimethamine

1. "Leucovorin rescue" for Methotrexate (MTX) Toxicity, or High-dose MTX therapy

Methotrexate is a dihydrofolate reductase inhibitor that prevents conversion of folic acid to its active form, tetrahydrofolic acid (FH_4), thereby decreasing purine synthesis and leading to cell death.

Risk factors associated with low-dose MTX-induced myelosuppression include volume depletion, renal insufficiency, age, hypoalbuminemia,

Indications for leucovorin "rescue" - High-dose MTX chemotherapy, MTX toxicity (N/V, pneumonitis, hepatotoxicity, myelosuppression, renal failure, etc.).

- Arbitrary indications for leucovorin rescue with MTX-induced myelosuppression: WBC < 3.5K, Plt < 140K, Hgb < 10g.
- Extracellular MTX levels may be misleading since intracellular accumulation can still cause myelosuppression despite low serum levels.
- Likewise, leucovorin primarily acts intracellularly and can reverse or bypass the toxic myelosuppressive effects of MTX even when serum MTX levels are low.

Dosage and method of administration: Do not use oral therapy.

Dosage determination is highly controversial.

1. Administer leucovorin intravenously a dose equal to or greater than the dose of MTX.

OR

2. If the MTX's dose is large but unknown, administer leucovorin 10 mg/m^2/dose (10-20mg) infused over 15-30 min q 6 hr for several days until MTX level is less than 0.01 mcmol/L. If MTX levels are unavailable, leucovorin should be continued for 12 to 24 doses (3 days) or longer.

Subsequent leucovolin therapy is guides by serum MTX levels as the following:

MTX concentration (mcmol/L)	**Hours after MTX exposure**	**Leucovorin dose (Adults and Children)***
0.1-1	24	10-15 mg/m^2 q 6 hr for 12 doses
1-5	24	50 mg/m^2 q 6 hr until the serum level is less than 0.1 mcmol/L
5-10	24	100 mg/m^2 q 6 hr until the serum level is less than 0.1 mcmol/L

* If serum creatinine increases by 50% in the first 24 hours after MTX, increase the dose frequency to every 3 hr until the MTX level is less than 5 mcmol/L

Bone marrow recovery typically occurs 1-2 weeks after recognition of MTX toxicity and initiation of leucovorin therapy.

$$\text{Body surface area, BSA } (m^2) = \sqrt{\frac{Ht(cm) \times (Wt\ (kg)}{3600}}$$

2. LEUCOVORIN for other folic acid antagonists that are less poten that MTX such as trimethoprim, pyrimethamine

Dosage and method of administration:

Leucovorin doses of 5 to 15 mg/day IM, IV, or PO for 5-7 days (Calcium folinate)

3. LEUCOVORIN for Methanol intoxication

Leucovorin may enhance the conversion of formic acid to CO2 and water.

Indication: in symptomatic patients (anion gap acidosis, visual disturbance) and asymptomatic patients with known or suspected methanol intoxication.

Dosage and method of administration:

Leucovorin doses of 1 mg/kg IV (up to 50 mg/dose) every 4 hours. (diluted in 100 mL of 5% dextrose in water and administered over 30-60 min)