Alert

Folinic acid is a 5-formyl derivative of tetrahydrofolic acid. It is not the same as folic acid, but does have an equivalent vitamin activity. Also known as calcium folinate or Leucovorin.

Indication

Concurrent therapy with dihydrofolate reductase inhibitors such as pyrimethamine to reduce bone marrow suppression [1, 2].

Folinic acid dependent seizures and secondary causes of cerebral folate deficiency including other inborn errors of metabolism [3, 4].

Action

Folinic acid is the active metabolite of folate that bypasses dihydrofolate reductase.

Drug Type

Metabolically active reduced form of folate (vitamin B9)

Trade Name

Leucovorin

Presentation

DBL Leucovorin Calcium tablets (calcium folinate) – 15 mg. Contains excipients including lactose monohydrate, microcrystalline cellulose, magnesium stearate.

DBL Leucovorin Injection (calcium folinate) – 15 mg/2 mL, 50 mg/5 mL, 100 mg/10 mL, 300 mg/30 mL strengths available.

Dosage/Interval

Concurrent therapy with dihydrofolate reductase inhibitors [1, 2]

- 10 mg three times per week
- Folinic acid responsive seizures [3, 5]
  - 2.5 mg twice a day (doses up to 8 mg/kg/day have been used)

Route

Oral

Maximum Daily Dose

Not established.

Preparation/Dilution

**Using the injection:**

- Measure the dose and give undiluted orally.

  **Using the tablet:**

  Add sterile water to 15 mg tablet to make it up to 15 mL suspension (1 mg/mL). Shake well before administration. Discard any unused liquid after administration.

Administration

Administer on an empty stomach (i.e. at least one hour before food or two hours after food). [13]

Monitoring

No specific monitoring required.

Contraindications

Little information. Not effective in methylenetetrahydrofolate reductase deficiency.

Precautions

Avoid use with folic acid antagonists unless under a specialist’s advice. [6]

Drug Interactions

Antiepileptics – folic acid may counteract the antiepileptic effect of phenobarbital (phenobarbitone), phenytoin, primidone and succinimides and increase the frequency of seizures.

Fluorouracil – folic acid may enhance the toxicity of fluorouracil.

Folic acid antagonists – when folic acid is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralised. [6]

Adverse Reactions

Allergic sensitisation, including anaphylactic reactions and urticarial rash. [6]

Nausea and vomiting with high doses.

Compatibility

Not applicable.

Incompatibility

Not applicable.

Stability

Oral dispersion made using tablets should be used as soon as possible and remaining liquid should be discarded.

Storage

Store below 25°C.

Special Comments

Evidence summary

**Efficacy**

**Concurrent therapy with dihydrofolate reductase inhibitors:**

*Pyrimethamine/sulfadiazine:* Current guidelines for treatment of the infant with congenital toxoplasmosis are for use of pyrimethamine and sulfadiazine plus folic acid [1, 2]. Folinic acid 10 mg three-times a week is recommended until 1 week following cessation of pyrimethamine treatment. It is advised not to use folic acid as a substitute for folic acid [1, 2]. Levels of folic acid in the CSF from folic acid supplemented infants treated with pyrimethamine for congenital toxoplasmosis are thought to be too low to inhibit the effect.
of pyrimethamine [7]. However, there are no clinical trials comparing folate or folinic acid versus placebo in infants with toxoplasmosis.

**Methotrexate**: Folate and folinic acid have a protective and probably similar effect against methotrexate-related adverse effects (including a reduction in gastrointestinal side effects, hepatic dysfunction and discontinuation of MTX treatment for any reason) in patients with inflammatory disease [8, 9].

**Trimethoprim/sulfamethoxazole**: There are no clinical trials comparing folate or folinic acid versus placebo in infants with toxoplasmosis.

**Folinic acid responsive seizures**

Folinic acid responsive epilepsies are caused by low concentrations of 5-methyltetrahydrofolate (MTHF) in the cerebrospinal fluid (CSF), which is associated with various neurological conditions. Genetic or autoimmune mechanisms cause cerebral folate deficiency and delayed treatment may lead to encephalopathy with severe learning disabilities. EEG may show abnormal background activity with multifocal spike-wave complexes, but typically has no diagnostic features. Neuroimaging results are also usually normal. Patients either do not respond to pyridoxine at all or exhibit only a temporary improvement. However, such patients show a marked neurological recovery including cessation of seizures upon folinic acid treatment [3, 5, 10]. In infants, folinic acid responsive seizures typically present within days after birth as epileptic spasms – myoclonic, absence or generalized tonic clonic seizures. Identified gene abnormalities include ALDH7A1, SLC46A1, FOLR1, MTHFR and MTHFS. Folinic acid 2.5 mg twice a day has been commenced with good effect in many case reports including one report with gradual increase of the dose over 14 months to 45 mg twice a day. [4, 5, 10-14] Recommended treatment includes initial treatment with folinic acid or 5-methyltetrahydrofolate 3–5 mg/kg and long-term treatment with folinic acid or 5-methyltetrahydrofolate 3–5 mg/kg daily [3].

**Safety**

No paediatric data are available.

References