TREATMENT OF DELAYED Mtx-CLEARANCE WITH VORAXAZE®

(Glucarpidase; formerly Carboxypeptidase G2)

Background

Methotrexate (Mtx) is a folic acid analog. It binds to dihydrofolate reductase and depletes cells of reduced folates (i.e. folinic acid). The efficacy of Mtx depends on the duration of this folinic acid depletion. Lack of reduced folates leads to death of normal hemopoietic cells after 42-48 hours, but probably earlier for Mtx-sensitive malignant cells. Folinic acid competes with Mtx in several biochemical pathways. Thus, the dosage of folinic acid dose should be titrated by the Mtx-concentration. This is generally effective, but also costly in case of very high Mtx concentrations. Furthermore, folinic acid is a *storage*-vitamin, and excessive rescue could thus interfere with the Mtx-efficacy at the next HD-Mtx course. In case of severe delayed Mtx-clearance the concentration may be life-threatening even with very high rescue doses of folinic acid. Dialysis can only reduce the plasma-Mtx concentration by approximately 50%, and marked rebound in Mtx concentration is common.

Drug type

VORAXAZE®, **Glucarpidase** ($GPDG_2$) is an enzyme that hydrolyses Mtx to non-toxic metabolites.

Provider

Protherics PLC (in the Nordic countries it is distributed by Swedish Orphan, see below)

Mode of action

Eliminates Mtx through conversion to glutamate and DAMPA (4-[[2.4-diamino-6-(pteridinyl) methyl]-methyl-amino]-benzoic acid), which is 25-100 times less toxic than Mtx. DAMPA and glutamate are excreted by the liver. $GPDG_2$ also cleaves folinic acid and may reduce the plasma levels by 50%. $GPDG_2$ preferentially cleaves Mtx.

Indications for $GPDG_2$ therapy

Delayed systemic Mtx-clearance: Mtx-treatment with $GPDG_2$ may be indicated in case of excessively high Mtx levels (e.g. 24 hour steady state levels > 250 µM (=250.000 nM), 36 hour levels > 30 µM (= 30.000 nM), or 42 hours levels >10 µM (=10.000 nM)). Not least in case reduced kidney function (>2 times the basic createnin value at the start of the high-dose Mtx-infusion) or anuria, which will generally be the case. Treatment with $GPDG_2$ may also be indicated in case of severe acute neurotoxicity during treatment with high-dose Mtx. Treatment with $GPDG_2$ should always be discussed with a pediatric oncologist, who is familiar with high-dose Mtx therapy. Treatment with $GPDG_2$ should optimally take place within 48 hours (max 60 hours) from the start of the Mtx-infusion, since the risk of life-threatening toxicities may not be reversible beyond this time point. Accidental excessive i.t. Mtx dosage: See below.

Drug form and administration

Lyophilized: 1 vial contains 1000 units. The vial is resuspended in 1ml of sterile water; and can be further diluted with isotonic saline (1:5 or 1:10). $GPDG_2$ is administered at a dose of 50 IU/kg over 3-5 min as intravenously by an infusion pump or by bolus injection. The rationale for use of Glucarpidase in MTX toxicity is based on the fact that the enzyme will hydrolyze the carboxyl terminal glutamate residue from compounds such as MTX, producing glutamate and DAMPA thas is metabolized by the liver, and thus use an alternative route of elimination.

The distribution volume of Glucarpidase is mainly to the blood volume. The elimination t½ is about 9-10 hours. Glucarpidase is therefore circulating in the blood for at least for 12 – 24 hours

$GPDG_2$ therapy:

1. Stop treatment with folinic acid 2-4 hours before $GPDG_2$, since $GPDG_2$ also breaks down folinic acid – see below.
2. Dosage: 50 Units/kg – always use the whole vial.
3. The powder is dissolved in sterile water. The solution is unstable and the drug should be given right after the solution has been made.
4. Administer $GPDG_2$ as a short infusion over 3-5 min by an infusion pump or by bolus injection.
5. Reinitiate folinic acid rescue after 6 - 12 hour after $GPDG_2$ administration
6. Hydration and urine alkalinization shall be continued normally until s-Mtx is $\leq$ 0.2 µM (200 nM).
7. Repeated administration of $GPDG_2$ during the same Mtx-course is not recommended due to decreased efficacy

Co administration of folinic acid (Leucovorin / Isovorin / Levofolinate):

Until $GPDG_2$ can be given give folinic acid according to the standard guidelines (e.g. according to NOPHO cMtx (µM) x body weight (kg) (= Leucovorin dose in mg). Due to the large quantities of Calcium, the infusion time of Leucovorin at doses > 0.5 gram should be 1–2 hours. To avoid the excessive Ca^{++}, Leucovorin can be substituted with Isovorin or Levofolinate that only contains the active L-form of folinic acid. Levofolinate is a sodium salt of folinic acid. The dose of folinic acid should then be reduced by 50 %. Continue treatment with folinic acid until cMtx $\leq$ 0.2 µM (= 200 nM). The minimal single dose of Leucovorin is 15 mg/m^2/dose. The minimal single dose of Levofolinate and Isovorin is 7½ mg/m^2/dose.

Treatment with folinic acid should be withheld for at least 2 - 4 hours prior to the administration of $GPDG_2$**,** as the efficacy may otherwise be significantly reduced. In case of life-threatening neurotoxicity, the interval between $GPDG_2$ and folinic acid administration can be reduced to 2 hours.
Folinic acid can be administered from 6 - 12 hour after the administration of $GPDG_2$ as Glucarpidase is circulating in the blood for at least for 12 – 24 hours. Continue folinic acid therapy until cMtx $\leq$ 0.2 µM (=200 nM). If you don't have access to HPLC-analysis of free cMtx you have to give folinic acid according to your routine measurement of cMtx (free Mtx and
DAMPA – see below). The reported half-life of DAMPA in humans is 9-12 hours.

cMtx measurements after $GPDG_2$

Within 15 min cMtx usually falls to 3% (range: 1% to 27%) of the pre- $GPDG_2$ concentration. However, many techniques for Mtx-measurements (but not HPLC) do not distinguish between the parent drug (Mtx) and the breakdown products (i.e. DAMPA). Hence, the post- $GPDG_2$ measured "Mtx-concentration" will frequently be 15% of the pre-$GPDG_2$ Mtx-concentration. Irrespective of method of measurement, use the measured Mtx-concentration to calculate the necessary dosage of folinic acid.

Accidental excessive i.t. Mtx dosage

In case of accidental excessive i.t. Mtx dosage $GPDG_2$ can be administered IT in a dosage of 2 000 Units. (This dose has been tested in children down to 6 years of age). The same dose is given irrespective of age.

Side effects

Rarely patients develop IgE antibodies to Glucarpidase, but anaphylaxes is rarely reported. A burning sensation, flushing, dermatitis and itching can be seen. Some may form inactivating IgG antibodies, which can be relevant in case of subsequent $GPDG_2$ administration.

Contraindications

Previous anaphylactic reactions to $GPDG_2$.

Contact persons with-in NOPHO

Clinicians within NOPHO could discuss the indication with NOPHOs Principal Investigator for Glucarpidase, Jesper Heldrup, Lund, Sweden (+46 705-17 23 89, jesper.heldrup@skane.se), Arja Harila-Saari, arja.harila-saari@oulu.fi phone +358 400 684 524 (Finland), +46 72 207 3530 (Sweden). or with the Principal National Investigator.

Availability

$GPDG_2$ is available at

1. Swedish Orphan v/Morten Borgersen, morten.borgersen@swedishorphan.com, Phone: +47 66 82 34 00 el. +47 913 31 260, Fax +47 66 88 23 401.
2. The Pharmacy, Rigshopitalet, Copenhagen. Outside normal working hours contact the pharmacist on call. Phone +45 35 45 35 45
3. Ward 51, Oulu University Hospital, Finland Phone +358 81 315 2011, or +358 8 315 5210
4. Apoteket C.W. Scheele; Box 1157; SE-111 81 Stockholm, Klarabergsgatan 64, Godsadress; Mäster Samuelsgatan 69, Phone +46 (0)8-454 81 25; +46 (0)70 202 89 72, Fax +46 (0)8-791 88 77
5. Ullevål University Hospital Pediatric department (two vials) Phone +47 22 11 81 97 Kirkeveien 166, 0450 Oslo Norway

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