Gäller för: Verksamhet Barncancercentrum, Verksamhet Onkologi
Innehållsansvar: Andreas Hallqvist, (andha16), Sektionschef
Granskad av: Andreas Hallqvist, (andha16), Sektionschef
Godkänd av: Johanna Svensson, (johsv6), Verksamhetschef

Giltig från: 2022-09-30
Giltig till: 2024-09-30

Lagerhållning Voraxaze (glukarpidas)

Revideringar i denna version

Beställningsförfarande av Voraxaze tillagt.

Syfte

Säkerställa lagerhållning och tillgänglighet av Voraxaze (glukarpidas) i västra götalandsregionen.

Arbetsbeskrivning

Voraxaze (glukarpidas) används vid enstaka tillfällen av fördröjd utsöndring/toxicitet av metotrexat. Läkemedlet levereras i ampuller om 1000 IU (1ml) där man doserar efter vikt och en vuxen person oftast behöver två ampuller. Man behöver aldrig ge mer än 2000 IU. För detaljer se bifogat appendix från Nordic Society of Paediatric Haematology and Oncology.

Verksamhet onkologi, Sahlgrenska ska alltid hålla minst två ampuller i lager så kan både barnonkologen och hematologen rekvirera från onkologen vid behov. Debiteras därefter via internfaktura.

Ampullerna förvaras på avd 69, onkologen, Sahlgrenska tel 031-342 10 69

Vid ev. kassation pga. utgånget datum delas kostnaden mellan inblandade kliniker. Observera att hållbarheten sannolikt är mycket längre än vad som oftast anges på förpackningen. Diskutera med ansvarig läkare innan kassation.

Beställning av Voraxaze från apoteket

Faxa en ifylld Beställningsblankett Licensläkemedel RGL.

Om kliniken inte har en generell licens för Voraxaze ska en sådan skickas in via KLAS-systemet.

Ansvar

Vårdenhetschef vid avd. 69 på onkologen ansvarar för att läkemedel lagerhålls, och att utlånad ampull debiteras.

Uppföljning, utvärdering och revision

Vårdenhetschef avd. 69 och läkemedelsansvarig läkare.

Relaterad information

Bifogat appendix om handhavande Voraxaze från Nordic Society of Paediatric Haematology and Oncology. Se nedan

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.

(Voraxaze 1 000 units/ML 1 AMP (755120) Product: Crofab (756924))

Provider

Clinigen Healthcare Ltd, London. Tel: +44 (0)1283 494340. Website: www.clinigengroup.com

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 GPDG2 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: One vial contains 1000 units. The vial is resuspended in 1 mL of sterile water; and can be further diluted with isotonic saline (1:5 or 1:10). $GPDG_2$ is administered at a dose of 25-50 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 that 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 24 hours.

$GPDG_2$ therapy:

1. Stop treatment with folinic acid before $GPDG_2$, since $GPDG_2$ also breaks down folinic acid – see below. If only a small dos of folinic acid has been given (15 mg/m²) give $GPDG_2$ directly
2. Dosage: 25-50 Units/kg – always use the whole vial. If you don't have 25-50 Units/kg but a lower dose – give what you have – don't wait. **Never give more than two vials**.
3. The powder is dissolved in 1 mL of sterile water and further diluted with isotonic saline (1:5 or 1:10). 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 bolus injection or by an infusion pump.
5. Reinitiate folinic acid rescue after 2-4 hour after $GPDG_2$ administration
6. Hydration and urine alkalinization shall be continued normally until s-Mtx is < 0.2 µM (200 nM). If you measure cMtx by chromatography (HPLC-analysis), remember to measure cMtx up to at least 48 hours after you have given Glucarpidase because of reentering of Mtx into the bloodstream from the tissues compartment.
7. Repeated administration of $GPDG_2$ with 48 hours during the same Mtx-course is not recommended due to decreased efficacy.

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

Until GPDG2 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 sodium Levofolinate that only contains the active L-form of folinic acid. Levofolinate is a sodium salt of folinic acid and can at any dose be given as a bolus dose. For Isovorin and sodium Levofolinate the dose of folinic acid should then be reduced by 50 %. Continue treatment with folinic acid until cMtx < 0.2 µM (= 200 nM). The minimal single dose of Leucovorin is 15 mg/m2/dose. The minimal single dose of Levofolinate and Isovorin is 7½ mg/m2/dose.

Treatment with folinic acid should be stopped prior to the administration of $GPDG_2$, as the efficacy may otherwise be significantly reduced.

Folinic acid can be administered from 2-4 hour after the administration of $GPDG_2$ as Glucarpidase is circulating in the blood for at least for 24 hours. Continue folinic acid therapy until cMtx < 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. Consult the NOPHO guideline: ***Accidental IT Mtx-overdose treated by intrathecal administration of Glucarpidase IT MTX overdoses in NOPHO Guideline 150205***

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 $GPDG_2$.

Availability

$GPDG_2$ is available at

Clinigen Healthcare Ltd
Pitcairn House,
Crown Square,
First Avenue,
Burton-on-Trent,

DE14 2WW
Tel: +44 (0)1283 494340
Website: www.clinigengroup.com
Ordering Details/Queries: International/Europe
Fax: +44 {0)1283 494341
Email: customer.services@clinigengroup.com

References:

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Dokumentation

Styrande dokument arkiveras i SOFIA STY. Redovisande dokument ska hanteras enligt sjukhusets gällande rutiner för arkivering av allmänna handlingar.

Granskare

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Information om handlingen

Handlingstyp: Rutin

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