Profile

Glucarpidase is a recombinant glutamate carboxypeptidase that hydrolyses methotrexate to inactive metabolites; it is under investigation for the management of methotrexate toxicity.

◊ References.

1. Widemann BC, *et al.* Carboxypeptidase-G2, thymidine, and leucovorin rescue in cancer patients with methotrexate-induced renal dysfunction. *J Clin Oncol* 1997; **15:** 2125–34.
2. Widemann BC, *et al.* Treatment of accidental intrathecal methotrexate overdose with intrathecal carboxypeptidase G2. *J Natl Cancer Inst* 2004; **96:** 1557–9.
3. Buchen S, *et al.* Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer* 2005; **92:** 480–7.

Glutathione *(BAN)*

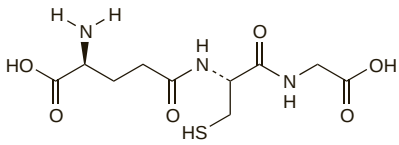
Glutathion; Glutathionum; Glutatión; Glutation; Glutationas; Glutationi; GSH. *N*-(*N*-L-γ-Glutamyl-L-cysteinyl)glycine.

$C_{10}H_{17}N_3O_6S$ = 307.3.

CAS — 70-18-8.

ATC — V03AB32.

ATC Vet — QV03AB32.



Pharmacopoeias. In *Eur.* (see p.vii) and *Jpn.*.

Ph. Eur. 6.2 (Glutathione). Fermentation product. A white or almost white, crystalline powder or colourless crystals. Freely soluble in water; very slightly soluble in alcohol and in dichloromethane. Protect from light.

Profile

Glutathione is an endogenous peptide with antoxidant and other metabolic functions. Glutathione and glutathione sodium are used to prevent neurotoxicity associated with cisplatin or oxaliplatin; they have also been used to prevent other adverse effects of antineoplastic and radiation therapy, as well as in a wide range of other disorders including poisoning with heavy metals and other compounds, liver disorders, corneal disorders, and eczema. Glutathione has also been tried in idiopathic pulmonary fibrosis and peripheral vascular disorders.

Antineoplastic toxicity. Glutathione has been reported to reduce the incidence of neurotoxicity induced by cisplatin therapy. In a double-blind, randomised trial[1] in 50 patients receiving cisplatin for advanced gastric cancer, glutathione significantly reduced the incidence of neuropathy assessed within one week of completing cisplatin therapy. There did not appear to be any reduction in cytotoxic activity. Similar benefit was observed in a randomised, double-blind, placebo-controlled trial involving 52 patients receiving oxaliplatin.[2]

1. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on cisplatin-based chemotherapy in advanced gastric cancer: a randomized double-blind placebo-controlled trial. *J Clin Oncol* 1995; **13:** 26–32.
2. Cascinu S, *et al.* Neuroprotective effect of reduced glutathione on oxaliplatin-based chemotherapy in advanced colorectal cancer: a randomized, double-blind, placebo-controlled trial. *J Clin Oncol* 2002; **20:** 3478–83.

Lung disorders. Glutathione is an important extracellular antoxidant in the lung and high concentrations are found in lung epithelial lining fluid. A deficiency of glutathione may contribute to the epithelial damage that occurs in various lung disorders, and treatment with nebulised glutathione has therefore been investigated. Small studies have found beneficial biochemical results in patients with cryptogenic fibrosing alveolitis (idiopathic pulmonary fibrosis)[1] and in cystic fibrosis,[2] but the clinical effects of these changes are not clear. Another study in cystic fibrosis[3] found no effect on oxidative markers after treatment for 2 weeks, but there was a small improvement in lung function. Benefit has also been reported[4] in a patient with emphysema. However, in a study[5] of patients with mild asthma, inhalation of glutathione solution was associated with bronchoconstriction, leading to cough or breathlessness in some patients, possibly due to sulfite formation.

1. Borok Z, *et al.* Effect of glutathione aerosol on oxidant-antioxidant imbalance in idiopathic pulmonary fibrosis. *Lancet* 1991; **338:** 215–16.
2. Roum JH, *et al.* Glutathione aerosol suppresses lung epithelial surface inflammatory cell-derived oxidants in cystic fibrosis. *J Appl Physiol* 1999; **87:** 438–43.
3. Griese M, *et al.* Improvement of alveolar glutathione and lung function but not oxidative state in cystic fibrosis. *Am J Respir Crit Care Med* 2004; **169:** 822–8.
4. Lamson DW, Brignall MS. The use of nebulized glutathione in the treatment of emphysema: a case report. *Altern Med Rev* 2000; **5:** 429–31.
5. Marrades RM, *et al.* Nebulized glutathione induces bronchoconstriction in patients with mild asthma. *Am J Respir Crit Care Med* 1997; **156:** 425–30.

Preparations

Proprietary Preparations (details are given in Part 3)

Hong Kong: Glu-tathion; TAD; ***Ital.:*** Eudon†; Glutanil†; Gluthion; Ipatox†; Maglut†; Reglumax†; Ridutox; Rition; Scavenger†; TAD; Tationil; Thioxene†; ***Jpn:*** Glutathin; ***Rus.:*** Glutoxim (Глутоксим); ***USA:*** Cachexon.

Multi-ingredient: ***Austral.:*** BSS Plus; ***Austria:*** BSS Plus; ***Canad.:*** BSS Plus; ***Fr.:*** BSS Plus; ***Ger.:*** BSS Plus; ***Hong Kong:*** BSS Plus†; ***Hung.:*** BSS Plus; ***Israel:*** BSS Plus; ***Malaysia:*** BSS Plus; ***Philipp.:*** Illumina; ***S.Afr.:*** BSS Plus; ***Singapore:*** BSS Plus; ***Switz.:*** BSS Plus†; ***Thai.:*** BSS Plus; ***USA:*** BSS Plus; Sucrets Defense Kids Formula; ***Venez.:*** BSS Plus†.

Haem Derivatives

Heme Derivatives; Hemo, derivados del grupo.

ATC — B06AB01 (Haematin).

ATC Vet — QB06AB01 (haematin).

Profile

Haem is the iron protoporphyrin constituent of haemoglobin and is responsible for its colour and oxygen-carrying capacity. It is used in the management of porphyrias (below). Haem is given intravenously as its derivatives, although there is some confusion over their terminology. The names haematin (hematin) and haemin (hemin) have been used interchangeably although chemically haematin is the hydroxy derivative, formed by the reaction of haemin and sodium carbonate in solution. The arginine salt (haem arginate; haemin arginate; heme arginate) is reported to be more stable.

Haem arginate is used in the treatment of acute hepatic porphyrias, including acute intermittent porphyria, variegate porphyria, and hereditary coproporphyria. It is given by slow intravenous infusion in a dose of 3 mg/kg daily for 4 days, infused over at least 30 minutes. The maximum recommended dose is 250 mg daily. The course may be repeated, with close monitoring, in patients with an inadequate response.

Haematin is used intravenously for the amelioration of acute intermittent porphyria associated with the menstrual cycle in patients unresponsive to other therapy. It is given in a usual dose of 1 to 4 mg/kg daily for 3 to 14 days as an intravenous infusion over 10 to 15 minutes. In severe cases the dose may be repeated after 12 hours, but no more than 6 mg/kg should be given in any 24 hour period.

Phlebitis may occur after infusion of haem derivatives and they should be given into a large arm vein or central vein. Use of a filter is recommended due to the colour of the infusion.

Porphyrias. The porphyrias are a group of inherited and acquired disorders of haem biosynthesis in which defects in specific enzymes lead to the accumulation of haem precursors, including aminolevulinic acid, porphobilinogen, and porphyrins.[1-11] They are generally classified as acute or non-acute, reflecting their clinical presentation, or as hepatic or erythropoietic, depending on the site of the enzyme defect. The three most common forms are acute intermittent porphyria, porphyria cutanea tarda, and erythropoietic protoporphyria.

ACUTE PORPHYRIAS. These are inherited disorders characterised by the accumulation of porphyrin precursors, leading to acute attacks of neurovisceral symptoms. The most common form is *acute intermittent porphyria* (acute hepatic porphyria); *variegate porphyria* and *hereditary coproporphyria* are generally less common forms in which there is accumulation of both porphyrin precursors and porphyrins, leading to acute attacks with cutaneous symptoms similar to those seen in non-acute porphyrias (see below).

In acute porphyrias, some enzyme activity is present and the defect only becomes apparent when demand for hepatic haem is increased. Attacks are rare before puberty and the disorder may remain latent in many patients. The presenting symptom is most commonly severe abdominal pain; other gastrointestinal symptoms such as nausea and vomiting also occur, along with autonomic effects including hypertension, tachycardia, sweating, pallor, and pyrexia. Convulsions may occur at the peak of an attack and may persist between attacks. Neuropathy leads to weakness and paralysis and may progress rapidly to respiratory distress. Psychiatric symptoms are also common, particularly agitation, anxiety, and behavioural disturbances. Various factors can increase the demand for haem and attacks are usually precipitated by drugs, alcohol, steroid hormones, reduced caloric intake, or infection. They typically last for several days and are followed by complete recovery, although in some patients chronic abdominal pain may persist without other symptoms.

The primary management of an attack is to remove precipitants and to provide intensive support. *Symptomatic treatment* is complicated by the wide range of drugs that may precipitate porphyria. High doses of parenteral opioids may be required for pain; there is a danger of addiction occurring, but this is rare unless attacks are frequent or pain persists between attacks. Phenothiazines such as chlorpromazine are useful to control nausea and agitation and their sedative effect may also be beneficial. High doses of propranolol may be required for cardiovascular symptoms. Assisted ventilation may be necessary. Convulsions usually disappear as the attack resolves; management of patients who experience convulsions between attacks is a therapeutic problem since many antiepileptics are porphyrinogenic (see Porphyria, p.471). *Specific therapy* is aimed at suppressing the haem biosynthetic pathway, to prevent further accumulation of precursors. Haem, given as either haematin or haem arginate, is the most effective treatment and should be given as soon as possible after onset of the attack; it produces feedback suppression of the biosynthetic pathway. Tin-protoporphyrin, a haem oxygenase inhibitor, has been given with haem to prolong its action but is not commercially available. A high carbohydrate intake may also suppress haem precursor production and should be ensured in all patients, especially if haem is not immediately available; it is usually given orally to prevent fluid overload and exacerbation of hyponatraemia, but intravenous glucose may be required in patients who are vomiting. *Prevention* of attacks involves avoiding drugs that precipitate porphyria and maintaining an adequate carbohydrate intake. Gonadorelin analogues, such as buserelin, may have a role in preventing attacks related to the menstrual cycle. Long-term treatment with haem has been tried in patients with frequent attacks, although such use is not established.

NON-ACUTE PORPHYRIAS. These are characterised by the accumulation of porphyrins and usually present with cutaneous symptoms, although porphyrins also accumulate in the liver and liver damage commonly occurs. *Porphyria cutanea tarda* (cutaneous hepatic porphyria) is the most common form of porphyria. It is usually an acquired disorder and in most cases there is a history of moderate or heavy alcohol intake. There is usually a raised serum-iron concentration and use of oestrogen has also been implicated. The main clinical symptom is cutaneous photosensitivity leading to bullous dermatosis, pruritus, and skin fragility, in areas exposed to sunlight. *Management* involves protecting the skin from sunlight and trauma and avoiding causative agents such as alcohol and iron. Sunscreen preparations must be based on zinc oxide or titanium dioxide to be effective. Reduction of serum-iron concentrations by phlebotomy restores enzyme function and is effective in most patients; it should be carried out every 1 to 2 weeks until remission occurs, and may be required periodically for maintenance. Chloroquine and hydroxychloroquine have also been used and may be effective where phlebotomy is contra-indicated; they appear to act by complexing with porphyrins and increasing their excretion, but low doses are necessary to avoid exacerbating the condition. An alternative method of reducing serum-iron is with the iron chelator desferrioxamine, although it may be less effective than phlebotomy; it is usually reserved for patients unable to tolerate phlebotomy. In patients with renal failure who are too anaemic for phlebotomy and who cannot excrete chloroquine, erythropoietin may be used, and may be combined with desferrioxamine or low-volume phlebotomy.

Erythropoietic protoporphyria is a less common non-acute porphyria and is an inherited disorder leading to accumulation of protoporphyrin. Symptoms are cutaneous and there is an acute reaction to sunlight leading to urticaria, pruritus, swelling, redness, and a severe burning sensation; liver damage may also occur. *Management* involves protection of the skin, as for porphyria cutanea tarda. Betacarotene is widely used to increase tolerance to sunlight, although its efficacy is not established; canthaxanthin, another carotenoid, has also been used. Haem administration, as haematin or haem arginate, may be beneficial in suppressing protoporphyrin production. Colestyramine and activated charcoal reduce protoporphyrin levels by interrupting enterohepatic recycling; they also bind other porphyrins and may have a role in rare forms of porphyria such as *congenital erythropoietic porphyria*.

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2. Thadani H, *et al.* Diagnosis and management of porphyria. *BMJ* 2000; **320:** 1647–51.
3. Sarkany RPE. The management of porphyria cutanea tarda. *Clin Exp Dermatol* 2001; **26:** 225–32.
4. Badminton MN, Elder GH. Management of acute and cutaneous porphyrias. *Int J Clin Pract* 2002; **56:** 272–8.
5. Murphy GM. Diagnosis and management of the erythropoietic porphyrias. *Dermatol Ther* 2003; **16:** 57–64.
6. Lecha M, *et al.* Diagnosis and treatment of the hepatic porphyrias. *Dermatol Ther* 2003; **16:** 65–72.
7. Kauppinen R. Porphyrias. *Lancet* 2005; **365:** 241–52.
8. Anderson KE, *et al.* Recommendations for the diagnosis and treatment of the acute porphyrias. *Ann Intern Med* 2005; **142:** 439–50. Correction. *ibid.*; **143:** 316.
9. European Porphyria Initiative. Information available at: http://www.porphyria-europe.com (accessed 04/10/05)
10. University of Cape Town Porphyria Service. Information available at: http://www.porphyria.uct.ac.za (accessed 04/10/05)
11. University of Queensland Porphyria Research Unit. Information available at: http://www.uq.edu.au/porphyria (accessed 04/10/05)