



NATIONAL ACUTE PORPHYRIA SERVICE (NAPS)

Best practice guidelines on: Clinical management of acute attacks of porphyria and their complications

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THE BRITISH AND IRISH PORPHYRIA NETWORK (BIPNET)

Best practice guidelines on: Clinical management of acute attacks of porphyria and their complications

1. Acute attacks

Clinical assessment:

Acute attacks of porphyria may occur in acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HCP). They are most common in young adults, and extremely rare before puberty. Females are more often affected than males. Patients are typically well between attacks. ALA dehydratase deficiency porphyria (ADP) is a very rare autosomal recessive porphyria; no cases have yet been described in the United Kingdom.

Clinical features during an attack:

- Abdominal pain - severe, poorly localised. Pain can also affect back, legs and other sites.
- Nausea, vomiting, constipation
- Dark urine - colour darkens to orange or red on exposure to light.
- Hypertension, tachycardia, and rarely, arrhythmias.
- Agitation, insomnia, confusion, psychosis with hallucinations and unusual behaviour.
- Convulsions - frequently associated with hyponatraemia.
- Peripheral motor neuropathy - may progress to flaccid paralysis, respiratory insufficiency, difficulty swallowing, urinary retention or incontinence
- Hyponatraemia
- Bullous skin lesions may be present during an acute of VP (about 50% of patients) or HCP (less than 20% of patients). Skin lesions do not occur in AIP.

Precipitating factors:

- Unsafe drugs - typically newly prescribed medication, including antibiotics, oral contraception, anticonvulsants. For information about drug safety in acute porphyria contact the Welsh Medicines Information Centre (see below).
- Alcohol
- Reduction in calorie intake e.g. fasting, dieting, gastrointestinal upset.
- Altered sex hormone balance, especially increased progesterone. Attacks in women are more frequent in the luteal phase of the

menstrual cycle. Pregnancy may trigger an attack but is usually well tolerated.

- Stress
- Infection
- Smoking
- Illicit drugs

Inheritance of AIP, VP and HCP is autosomal dominant, so a history may reveal an affected relative. However most carriers of the gene defect are likely to remain asymptomatic (penetrance is incomplete).

Initial investigations

| Test | Sample | Laboratory | Reason |
|--|---|---|-------------------------------------|
| Urine porphobilinogen (PBG) ¹ and total porphyrin | 10 ml urine in plain bottle, must be protected from light | Check local Clinical Chemistry laboratory for test availability | Confirm diagnosis ^{2,3} |
| Electrolytes, creatinine, urea | Plasma | Routine Clinical Chemistry | Detect hyponatraemia or dehydration |
| Full blood count | Whole blood | Routine Haematology | Detect infection |

Other investigations as indicated, such as

| Test | Indication |
|---|-----------------------------------|
| Blood and urine cultures, chest X-ray, C-reactive protein | Severe attack, possible infection |
| Serum and urine osmolalities, urine sodium | Hyponatraemia |
| Magnesium | Severe attack, convulsions |
| Liver function tests ⁴ | Severe attack, alcohol, drugs |
| Clotting screen | Severe attack |
| ECG | Tachycardia, arrhythmia |
| EEG, brain MRI | Encephalopathy, convulsions |

¹ PBG analysis, preferably by a quantitative test, is essential. A positive result in a qualitative or semi-quantitative screening test must be followed by urgent PBG quantitation. However in a severely ill patient, treatment should not be delayed.

² Urine PBG concentration is always raised in an acute attack of porphyria. Some patients with acute porphyria (especially AIP) have persistently elevated urine PBG concentrations. Interpretation of results in such patients is complex as it requires comparison with a recent baseline quantitative PBG:creatinine ratio in conjunction with clinical assessment. PBG is not

increased in ADP and urine ALA should also be measured in children if acute porphyria is suspected.

³ Urine PBG excretion may return to normal relatively quickly in VP and HCP. Where there is a delay in sample collection, PBG measurement alone is not sufficient to exclude acute porphyria; analysis of faecal and plasma porphyrins is essential.

⁴ Liver function is not affected in acute porphyria. Increased transaminase activity may be evidence of rhabdomyolysis, which can be diagnosed by measuring creatine kinase.

Management of an acute attack:

Specific treatment is indicated only in patients with clinical features of an acute attack **and** increased excretion of porphobilinogen in the urine. In mild attacks, a high carbohydrate diet and supportive measures may be used for up to 48 hours. However if neurological complications occur in the absence of other indicators of severity, treatment with haem arginate should be started immediately

Patients with severe attacks should be admitted to hospital for evaluation, control of symptoms, and prompt treatment of complications. Symptoms usually improve within a few days of starting haem arginate, and most patients make a complete recovery in 1-2 weeks. Patients with neurological complications (convulsions, progressive neuropathy, respiratory insufficiency, encephalopathy), severe hyponatraemia (plasma sodium less than 120 mmol/L) or cardiac arrhythmias must be cared for in a High Dependency or Intensive Care Unit (see section 2 below).

Remove precipitating factors: Review medication and check for safety in acute porphyria. New medication is a common trigger. Look for, and treat, infection.

Consider other causes of symptoms: For instance, abdominal pain in a patient with porphyria may be due to appendicitis, cholecystitis or a complication of pregnancy. Surgical or other appropriate opinions should be sought if other diagnoses are thought possible.

Haem arginate: Intravenous haem arginate reduces production of porphyrins and their precursors, ALA and porphobilinogen, by repressing hepatic ALA synthase activity. Many clinical trials suggest that acute attacks respond favourably to haem arginate, though the only placebo controlled double blind trial (involving 12 patients) gave a statistically insignificant result (Herrick *et al*, 1989). Early treatment with haem is associated with significantly improved outcome (Mustajoki and Nordmann, 1993).

Indications for haem arginate in acute porphyria include severe or prolonged pain, persistent vomiting, hyponatraemia, convulsions, psychosis or neuropathy. See Appendix A for details of administration. Haem arginate has

been administered in pregnancy and appears to be safe (Marsden and Rees, 2010).

Haem arginate is irritant to veins, and repetitive peripheral use may lead to loss of the superficial venous system. It is therefore very important to infuse through a large vein, and to alternate arms for daily infusions. Administration advice must be followed carefully, particularly after the infusion:

- After the haem arginate has run through, immediately rinse vein with 250ml 0.9% NaCl (initially 3-4 boluses of 10ml, then infuse remainder)
- Remove venous cannula.

Although there is no published evidence, these problems may be reduced by diluting haem arginate in albumin rather than in saline. The use of 20% albumin provides a 1:1 molar ratio of albumin to haem and should ensure binding of all haem molecules, since each molecule of albumin has a single high affinity haem binding site (Anderson *et al.*, 2006).

Analgesia: Analgesia should be given as soon as possible. Seek support from a pain team where available. Patients with severe attacks require opiates to control their pain, and analgesic requirements are typically high. Morphine, diamorphine and fentanyl are safe, but pethidine should be avoided in this situation, as metabolites may be associated with seizures. Consider use of a Patient Controlled Analgesia (PCA) pump to deliver an intravenous opiate with a prophylactic antiemetic. Opiates should be replaced by less addictive analgesics as early as possible and should not be dispensed after discharge from hospital.

Other medication: All drugs given to the patient should be checked for their safety in acute porphyrias. The Welsh Medicines Information Service provides advice and a list of safe drugs:

website: www.wmic.wales.nhs.uk/porphyria_info.php

Tel: 029 2074 3877 or 029 2074 2251

Email: welshmedicines.information@cardiffandvale.wales.nhs.uk

- a. Nausea and vomiting can be treated with prochlorperazine, promazine or ondansetron.
- b. Severe agitation and anxiety can be treated with chlorpromazine.
- c. Hypertension and tachycardia may be cautiously treated with atenolol, propranolol or labetalol (but monitor for hypotension and bradycardia).
- d. Convulsions can be terminated with intravenous diazepam[#], clonazepam or magnesium sulphate.

Although safety of diazepam is controversial, benefit outweighs risk when used in this acute situation. However safer anxiolytics should be prescribed for ongoing use.

Nutrition: Carbohydrate loading was the standard treatment for an acute attack prior to the availability of haem arginate. Glucose has a repressive effect on ALA synthase through effects on peroxisome proliferator-activated

receptor gamma coactivator 1-alpha (Handschin *et al.*, 2005). Mild attacks (mild pain, no vomiting, no paralysis, no hyponatraemia) may be aborted by increasing oral carbohydrate intake with the use of glucose containing drinks and high-energy foods.

In more severe attacks where oral intake is poor, for instance due to vomiting, and intravenous fluid therapy is required, 0.9% sodium chloride containing 5% glucose can be given intravenously at a rate of 2 litres per 24 hours. Experience from several specialist porphyria centres indicates that this practice can prevent the development of severe hyponatraemia (Hift and Meissner 2005; Puy *et al.* 2010). **Intravenous glucose in water solutions, such as dextrose 5% or 10%, should be avoided as they may aggravate hyponatraemia.** Intravenous glucose has no role in the treatment of an acute attack once treatment with haem arginate has commenced.

Fluid balance: Monitor fluid balance. Intravenous fluid replacement with 0.9% sodium chloride may be required to correct dehydration or electrolyte imbalance. Hyponatraemia should be corrected slowly (less than 6 mmol/L in 24 hours) to minimise the risk of central pontine myelinolysis. Fluid restriction is not appropriate, as hyponatraemia is at least partly due to renal sodium loss. See above for use of intravenous glucose.

Cardiovascular function: Pulse and blood pressure should be checked at least 4 hourly. An ECG monitor should be used to check for arrhythmias in patients with a tachycardia.

Respiratory function: Monitor respiratory rate, vital capacity, and blood gases in severe attacks. Evidence of respiratory insufficiency requires immediate transfer to an Intensive Care Unit for intubation and positive pressure ventilation.

Neurological function: Monitor for signs of neuropathy, including muscle strength, bladder and bowel function.

Monitoring blood tests should include:

| Test | Frequency (at least) |
|--------------------------------|--|
| Electrolytes, urea, creatinine | Daily (Every 8-12 hours if iv fluids or hyponatraemia) |
| Full blood count | Twice weekly |
| Calcium, magnesium | Twice weekly |
| Liver function tests | Twice weekly |
| C-reactive protein | Twice weekly |

2. Severe acute attacks with neuropathy

Severe attacks with neuropathy are almost always a consequence of delayed diagnosis and/or delayed treatment. Neuropathy usually develops in the context of pre-existing abdominal pain, and other clinical features of a severe

acute attack. A symmetrical motor neuropathy with weakness beginning proximally in the upper limbs is typical. Focal neuropathy can also occur, and may involve cranial nerves. Neuropathy may progress rapidly to give complete paralysis, incontinence or urinary retention, swallowing difficulties and respiratory failure. Sensory neuropathy is uncommon.

Management of a severe attack with neuropathy:

Progressive neuropathy is a medical emergency, and care of such patients must initially take place in a High Dependency or Intensive Care Unit, with access to specialist Metabolic and Neurology advice. Management should involve a multidisciplinary approach with monitoring of all organ systems and appropriate support. Infections are the main complication in critically ill patients and should be treated promptly and aggressively. Care can be transferred to general Neurology or Rehabilitation services after the acute attack has subsided, provided the patient does not require respiratory support.

Haem arginate: Patients with neuropathy must be treated with haem arginate as soon as possible. Although haem arginate will not reverse an established neuropathy, it will prevent further neuronal damage. In a severely ill patient, courses of haem arginate longer than 4 days may be indicated, although there is no good evidence that this improves outcome. Longer courses should be considered in patients with advanced neurological damage with the aim of suppressing progression. The optimum dose, frequency and duration are uncertain, but treatment periods as long as 3 months have been undertaken occasionally. A daily infusion at 3 mg/kg is advisable initially, with gradual reduction of either the dose or frequency of infusions as the patient recovers. Relapse is likely on stopping long-term haem arginate, and most patients need a maintenance dose, for instance a weekly haem arginate infusion, for a long period.

Respiratory support: Artificial ventilation may be necessary for several months if respiratory failure has occurred.

Physiotherapy and occupational therapy: Recovery from neuropathy occurs slowly and may be incomplete. Intensive physiotherapy should be started as soon as possible to optimise recovery of function. Even advanced paralysis is potentially reversible though it may require months of rehabilitation. At a later date, occupational therapy is important to help the patient achieve independence and minimise long-term disability.

Neuropathic pain: Gabapentin and opiate patches may be useful to control neuropathic pain during recovery.

Safe medication: In the setting of an Intensive Care Unit with many staff from different disciplines involved inpatient care, it is particularly important to check all medication for safety in acute porphyria. Prescription of an unsafe drug in a patient who is already seriously ill with an acute attack must be avoided.

Clear reminders both above the patient's bed and attached to the drug chart, as well as a suitable wrist-band are useful.

Nutritional support: Good nutrition by enteral or parenteral routes is essential to prevent catabolism and reduce the risk of further attacks. Specialist Dietetic advice should be sought. Folic acid and vitamin B₁₂ may require supplementation. Vitamin D deficiency is likely in a patient who has been hospitalised for many months. Iron status should be monitored. The patient should be weighed weekly.

Psychiatric support: Many patients are young women who have previously led healthy and fulfilling lives. Psychiatric problems including depression are common and should be managed appropriately. Note that fluoxetine is safe in acute porphyria, but tricyclic antidepressants are not safe. Patients may also benefit from referral to a Clinical Psychologist for counselling and support.

Monitoring in severe attacks with prolonged hospital admission:

| Test | Suggested Frequency |
|-----------------------------------|---|
| Full blood count | Daily |
| Electrolytes, urea, creatinine | Daily |
| Liver function tests | Twice weekly |
| Calcium, phosphate, magnesium | Twice weekly |
| Clotting function | Twice weekly |
| C-reactive protein | Twice weekly |
| Vitamin D | When indicated |
| Folic acid and B ₁₂ | Monthly |
| Iron, Ferritin | Monthly |
| Quantitative urine PBG and/or ALA | Levels suppressed by haem arginate, but may not reflect clinical response. May be useful if reducing haem arginate. |

3. Recurrent acute attacks

A minority of patients have recurrent acute attacks of porphyria. In women, attacks are typically related to the menstrual cycle.

Management of recurrent acute attacks:

General measures and avoidance of precipitating factors: Patients should be educated regarding precipitating factors. Regular meals, and avoidance of smoking, alcohol, and drugs that can induce attacks, are all relevant. Symptomatic treatment of nausea and loss of appetite is important to help ensure an adequate diet. Patients should be given a letter or other document giving details of their condition and recommended treatment. They should be given information about appropriate support groups such as the

British Porphyria Association. All patients with recurrent attacks should be referred to a specialist porphyria centre for advice on management and long-term monitoring.

Luteinising hormone-releasing hormone analogues: In women with recurrent pre-menstrual attacks of porphyria, Zoladex 3.6 (containing goserelin acetate 3.6 mg) a long acting analogue of luteinising hormone-releasing hormone, can be administered to prevent ovulation. The implant is given by subcutaneous injection into the anterior abdominal wall every 28 days, with the first injection being given during the first few days of the menstrual cycle. NOTE Administration of gonadotrophin releasing hormone analogues may induce a hormone surge that can trigger an acute attack. Side effects include depression, hot flushes, reduced libido, osteoporosis and other menopausal symptoms. These can be reduced by use of a low dose oestrogen patch. Regular gynaecological review, and annual bone density determinations should be arranged. Treatment with gonadotrophin releasing hormone analogues should be reviewed after one year.

Prophylactic haem arginate: Haem arginate is not licensed as a preventative treatment, but it has been useful in some patients in whom quality of life is severely impaired by frequent, recurrent attacks that are unresponsive to the above measures. Problems include complications related to venous access devices, iron overload associated with long term use, (which can be managed with venesection) and difficulty withdrawing treatment. The decision to commence regular haem arginate should be made only by specialist metabolic centres with experience in this therapy and facilities for follow up and monitoring. Administration through a central line is preferable. This should be inserted and managed by clinical staff with experience in the field of vascular access. Prophylactic haem arginate should be given at the lowest possible frequency that is effective. In patients with pre-menstrual attacks, one infusion of haem arginate (or two infusions on consecutive days) at an appropriate point in the second half of the cycle may be sufficient. Home therapy supervised by one of the homecare nursing companies may be possible for some patients, and will minimise disruption to daily life.

Liver Transplantation: Liver transplantation has been undertaken in 10 AIP patients in the UK and Ireland and is curative, resulting in biochemical and clinical remission (Soonawalla *et al.*, 2007, Dowman *et al.*, 2011). Indications include: intractable acute attacks not responsive to medical treatment, recurrent acute attacks severely affecting quality of life, repeated severe life threatening acute attacks leading to prolonged ventilation, lack of venous access for haem arginate treatment. Morbidity and mortality after transplantation is dependent on the level of preoperative complications and organ damage (paralysis, contractures, technical difficulty due to large vein thromboses).

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Clinical management of acute porphyria

British and Irish Porphyria Network (BIPNET)
National Acute Porphyria Service
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APPENDIX A

Haem arginate (Normosang¹)

| | |
|-----------------|---|
| Dose | 3 mg/kg once daily for 4 consecutive days by slow iv infusion. (May be repeated if clinical response to first course is inadequate). Maximum dose should not exceed 250 mg or 5 mg/kg daily. |
| Strength | 25 mg/ml concentrate, in 10 ml vials. Each vial contains 250 mg human hemin, 267 mg arginine, 1 g ethanol, 4 g propylene glycol, water. |
| Storage | Refrigerate at 2-8 °C, protect from light. |
| Stability | Unopened vials are stable for two years if properly stored. Diluted haem arginate should be used within 1 hour and protected from light. Discard unused concentrate. |
| Infusion | Add required volume of haem arginate concentrate (25 mg/ml) to 100 ml of human albumin (4-20%) or sodium chloride (0.9%) in a sterile glass bottle. Do not shake. Connect to giving set with 15-20 micron inline filter. Infuse within 1 hour (maximum rate 2 ml/min) via central line, central port or large peripheral vein. After infusion, flush vein with 250 ml sodium chloride 0.9% (first with 3-4 boluses of 10 ml, then infuse remaining solution under gravity). |
| Adverse effects | Thrombophlebitis (<1%); hypersensitivity (very rare); iron overload in patients receiving frequent haem arginate over long periods. |

¹ Normosang is available from Orphan Europe, Isis House, 43 Station Road, Henley-on-Thames, Oxfordshire, RG9 1AT; Tel:01491-414333; Fax: 01491414-443; email: infoUK@orphan-europe.com