Treatment of acute porphyria

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Haem preparations are now available for the specific treatment of attacks of acute porphyria. This review focuses on their use in this uncommon but life-threatening medical emergency.

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Acute attacks occur in four porphyrias (Kappas et al, 1995) (*Table 1*). The main clinical features are summarized in *Table 2*. Acute attacks, which are often provoked by drugs, hormones, alcohol or calorie restriction, are commoner in women, usually first occur between the ages of 15 and 40 years and are very rare before puberty (Kappas et al, 1995; Elder et al, 1997; Kalman and Bonkovsky, 1998; Thadani et al, 2000). The diagnosis of an acute attack of porphyria requires demonstration of increased urinary excretion of the haem precursor, porphobilinogen (PBG). Further investigation is needed to identify the type of porphyria (*Table 1*), but this should not be allowed to delay treatment. The prevention of acute attacks by family screening and counselling of affected individuals is reviewed elsewhere (Elder et al, 1997; Thaddani et al, 2000).

TABLE 1.
Main features of the acute porphyrias

Porphyria	Feature
Acute intermittent porphyria	Low penetrance autosomal dominant
	Commonest acute porphyria
	No skin lesions
	Increased urinary PBG, ALA
	Normal faecal coproporphyrin and protoporphyrin
Hereditary coproporphyria	Low penetrance autosomal dominant
	Acute attacks with blisters
	Skin fragility in about one third of patients
	Increased urinary PBG, ALA
	Increased faecal coproporphyrin III
Variegate porphyria	Low penetrance autosomal dominant
	About 20–30% of patients present with acute attacks of which about half also have blisters
	Skin fragility, 70–80% have skin lesions alone
	Increased urinary PBG, ALA during acute attack
	Increased faecal protoporphyrin and coproporphyrin III
5-aminolevulinate synthase dehydratase deficiency porphyria	Very rare autosomal recessive disorder presenting at any age with acute attacks, neuropathy or both
	Increased urinary ALA

ALA = 5-aminolevulinate; PBG = porphobilinogen

SUPPORTIVE TREATMENT

As soon as an acute attack of porphyria is suspected as the cause of illness, any drugs or other potential provoking agents should be withdrawn and appropriate supportive treatments started using drugs that are safe in acute porphyria (*Table 3*) (Gorchein, 1997). At the same time, urinary PBG excretion must be measured by a specific, quantitative technique. If it is normal, an acute attack of porphyria is unlikely. Urinary coporporphyrin excretion is often increased in acutely ill patients and by itself does not indicate acute porphyria (Bonkovsky and Barnard, 1998; Elder et al, 1990).

Opiates are the most effective analgesics for use in an acute attack. Simple analgesics, such as aspirin, paracetamol and codeine, are usually ineffective. Since acute attacks are usually short lived and infrequent, opiates may be used in high doses without fear of addiction. Chlorpromazine

TABLE 2.
Clinical features of acute porphyria

Symptom/sign	Per cent of acute attacks (*n*=143)
Abdominal pain	97
Non-abdominal pain	25
Vomiting	85
Constipation	46
Psychological symptoms	8
Convulsions	5
Muscle weakness	8
Sensory loss	2
Hypertension (diastolic >85 mmHg)	64
Tachycardia (>80 per minute)	65
Hyponatraemia (<135 nmol/litre)	37

Data from Mustajoki and Nordmann (1993); RJ Hift, unpublished data, 1986–95

or promazine may help decrease the requirement for analgesics. In some patients, residual neuropathic pain continues once the acute attack has settled. Typically, such pain is felt in the back, thighs and shoulders. It may be associated with autonomic symptoms, such as cool extremities and excessive sweating. It is important to recognize that this pain differs from that of the acute attack itself and, wherever possible, to avoid using addictive analgesics for its management.

Hyponatraemia is common and may be severe enough to provoke convulsions. Although it is usually attributed to inappropriate secretion of antidiuretic hormone, some patients may have renal sodium loss in addition to impaired ability to excrete a water load. Severe hyponatraemia may develop rapidly, particularly in response to large volumes of hypotonic intravenous fluids (Kalman and Bonkovsky, 1998). Careful management of intravenous fluids, with electrolyte measurement at least twice daily, and avoidance of hypotonic solutions whenever possible, is essential. Hyponatraemia should be corrected slowly; patients with acute attacks seem particularly liable to develop cerebral oedema and osmotic demyelination. Restriction of water intake to around 500 ml per day may be sufficient alone, but if symptoms necessitate isotonic or hypertonic saline, the rate of correction should not exceed 8 mmol/litre within any 24-hour period (Adrogue and Madias, 2000).

Cardiovascular complications, such as hypertension and tachycardia, are rarely sufficiently severe to require therapy in their own right. Very occasionally, the acute attack is accompanied by a severe adrenergic crisis with dangerous hypertension, encephalopathy, seizures and ischaemic changes seen on computed tomography brain scanning. Intravenous infusions of magnesium sulphate are effective in controlling the adrenergic symptoms; haem arginate therapy must be administered to abort the attack. The onset of a motor neuropathy is often marked by severe pain and stiffness in the thighs and back, followed by loss of tendon reflexes and motor paralysis. When vital capacity becomes severely reduced by paralysis of the intercostal muscles, artificial ventilation is necessary and may have to be continued for several months until the expected eventual recovery occurs.

Since impaired nutrition may aggravate porphyria, it is important to ensure that adequate calories are given (Robert et al, 1994). They are preferably given as carbohydrate-rich food supplements orally or, if necessary, via a nasogastric tube. Where vomiting precludes enteral administration, some carbohydrate may be provided as normal saline with 5% dextrose, 2 litres of which provide 100 g of glucose per day. Avoid infusing large volumes of hypotonic dextrose as this aggravates hyponatraemia. As soon as patients are able to take food orally, they should be transferred to a diet in which carbohydrate provides 55–60% of the energy needed to maintain a normal weight.

SPECIFIC TREATMENT

All attacks of acute porphyria are associated with increased activity of hepatic 5-aminolevulinate (ALA) synthase, overproduction of ALA and relative haem deficiency in the liver. The relation between these biochemical abnormalities and the neuronal dysfunction that underlies all features of the acute attack is uncertain (Lindberg et al, 1999). Two procedures that decrease hepatic ALA synthase activity in laboratory animals, carbohydrate loading (Brodie et al, 1977) and parenteral administration of haem (Bonkovsky, 1993), have been used successfully for the specific treatment of attacks of acute porphyria. Haem also corrects any haem deficiency in the liver.

Specific treatment should be started as soon as the diagnosis is established unless the attack is mild and clearly resolving. Neither carbohydrate loading nor intravenous haem will reverse an established peripheral neuropathy, although haem may prevent its onset and may possibly halt further progression of neuropathy if given sufficiently early.

TABLE 3.
Supportive treatment of acute attack

Indication	Drugs or other procedure
Pain	Paracetamol
	Dihydrocodeine
	Pethidine
	Diamorphine
Vomiting	Promazine
	Prochlorperazine
Sedation, decrease analgesic requirement	Chlorpromazine
	Promazine
Convulsions	Correct hyponatraemia*
	Intravenous diazepam
	Clonazepam
	Magnesium sulphate
Hypertension/tachycardia	Propranolol†
Muscle weakness/paralysis	Monitor progress
	Early physiotherapy
Constipation	Bulk-forming laxatives
	Senna

*see text; †even low doses may provoke severe hypotension and bradycardia (Kalman and Bonkovsky, 1998)

Carbohydrate loading

Before the introduction of haem, carbohydrate loading was the only form of therapy for the acute attack; a recommended regimen being 2 litres of 20% glucose over 24 hours in divided doses of 500 ml through a central venous catheter (Brodie et al, 1977). Where haem preparations are available, such high doses of carbohydrate are no longer necessary.

Haem preparations

The therapeutic effect of haem in acute porphyria was first described in 1971 (Bonkovsky et al, 1971), but subsequent use has been limited by difficulties in preparing stable solutions for intravenous use. In 1987, haem arginate (Normosang; Orphan Europe, Paris) was introduced and is now licensed in nineteen countries, including the UK. Haem is available as a lyophilized powder (Panhematin; Abbott Laboratories, North Chicago, Il) in the USA where haem arginate does not have Food and Drug Administration approval.

Normosang is a concentrated haem solution (250 mg haem per ampoule) in which haem is stabilized as a complex with arginine (267 mg) suspended in a mixture of ethanol (1g) and propyleneglycol (4 g) made up to 10 ml with water. The recommended dose is 3 mg/kg body weight/day, up to a maximum of 250 mg, given for 4 consecutive days. It is often convenient to use a dose of 250 mg for adults irrespective of their weight. Most patients improve within 5 days, but, if necessary, the course may be repeated after a day or two (although the effectiveness of prolonged treatment has not been evaluated). The concentrated haem arginate solution should be mixed with 100 ml physiological saline in a glass container immediately before infusion into a large peripheral vein or through a central venous line over 15–20 minutes. Once diluted, the haem becomes unstable and may aggregate if there is undue delay. After infusion, the vein should be flushed with saline for 10–15 minutes.

Haem should be given as soon after the onset of the attack as practicable (Mustajoki and Nordmann, 1993). In a mild attack, it may be acceptable to allow 24 hours for spontaneous settling of the attack. However, haem arginate should be given promptly, if possible within 24 hours of admission, to any patient with severe symptoms, or who shows complications such as seizures, hyponatraemia or features suggestive of incipient neuropathy, and also to any patient with a history of a previous attack complicated by neuropathy. If delay is unavoidable, glucose may be given as described above. Monitoring the metabolic effect of haem arginate by daily measurement of urinary ALA or PBG excretion is often recommended but in practice has little benefit.

How good is the evidence that haem arginate is effective? That it has a profound metabolic effect is not disputed (Tenhunen and Mustajoki, 1998). ALA excretion is markedly decreased, presumably by haem-mediated inhibition of synthesis of hepatic ALA synthase. Its effect on clinical outcome has been more difficult to establish. The only controlled trial, a double-blind study comparing placebo and haem arginate in 12 patients, found a trend in favour of haem arginate for total analgesic requirement and duration of hospital stay, but differences did not reach statistical significance (Herrick et al, 1989). A study of 51 consecutive acute attacks in 24 patients, using similar outcome measures but no control group, concluded that the outcome was better than in any previously published series (Mustajoki and Nordmann, 1993). Since these studies were published, experience with haem arginate has accumulated, but the evidence that it is effective still remains largely based on the combined experience of specialist centres (Tenhunen and Mustajoki, 1998).

The short-term use of haem arginate appears to be safe (Tenhunen and Mustajoki, 1998). The coagulopathies reported with other haematin preparations do not occur. Although thrombophlebitis at peripheral vein infusion sites has been reported in less than 1% of cases, the authors' own experience is that it is much commoner. Administration in 20% human serum albumin greatly reduces the incidence of phlebitis. Hypersensitivity reactions are very rare. Attacks during pregnancy have been treated without any apparent adverse effects on mother or child. Each 250 mg dose of haem contains 22.7 mg of iron; about one tenth of the iron in one unit of blood. Iron overload is therefore a potential problem only in patients treated on numerous occasions.

Hepatic haem is catabolised by haem oxygenase-1 (HO-1), a microsomal enzyme that is itself induced by haem. Addition of an HO-1 inhibitor, such as tin protoporphyrin or zinc mesoporphyrin, may be useful in the treatment of patients who do not respond to haem (Bonkovsky, 1993; Dover et al, 1993). When co-administered with haem arginate, tin protoporphyrin is no more effective than haem arginate alone in reducing ALA and PBG excretion but may induce a longer biochemical remission (Dover et al, 1993). The authors' experience with two patients with recurrent attacks of acute intermittent porphyria that required repeated haem arginate administration at short intervals sug-

gested that this might have induced tolerance to the haem arginate. Under these circumstances, co-administration with tin protopoporphyrin appeared to restore efficacy (Elder et al, 1997). Tin protoporphyrin has toxic effects, in addition to being a potent photosensitizer, and zinc mesoporphyrin has therefore been suggested as an alternative (Bonkovsky, 1993). Neither is widely available, and experience with their use is restricted to a very few specialist centres.

MANAGEMENT OF REPEATED ACUTE ATTACKS

A minority of patients have repeated acute attacks. Women with cyclical premenstrual attacks may respond to suppression of ovulation with gonadorelin analogues (Anderson et al, 1990). If this is successful, it can be continued for up to 2 years before attempting withdrawal. In those who respond, low-dose oestrogen replacement, preferably with patches, reduces the likelihood of osteoporosis and appears to have a low risk of provoking acute porphyria. Progestogen administration is potentially hazardous. Regular monitoring for endometrial hyperplasia is also required.

Otherwise, management of repeated attacks severe enough to require hospitalization is difficult. The main objectives are to facilitate prompt administration of haem arginate as required and to use analgesia in a way that minimizes the risk of addiction, as the combination of recurrent symptoms of porphyria and opiate addiction is particularly difficult to manage. It may be possible to abort the development of an attack by prompt administration of haem arginate for 1 or 2 days without the need for a full course. Regular once- or twice-weekly administration of a single dose may help control the disease. Such patients are likely to require permanent indwelling venous catheters with all their attendant complications. A few patients have now received very large cumulative doses of haem arginate without serious side-effects, although hepatic iron overload has been observed. Withdrawal of haem arginate from those whose disease is controlled is a difficult problem that has not yet been solved.

CONCLUSION

The introduction of a relatively stable preparation of haem, haem arginate, has substantially improved the treatments of acute attacks of porphyria. Haem arginate has a greater metabolic effect and leads to a better clinical outcome than carbohydrate loading. It is easier to administer, avoids the danger of water overload and has very few side effects. It should replace glucose loading as the specific treatment for acute porphyria, but, since it supplies no calories, appropriate nutritional support is needed for severely ill patients. HM

Conflict of interest: Professor Elder is a member of the UK Porphyria Interest Group, which is supported by Orphan Europe.

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KEY POINTS

- An acute attack of porphyria is a life-threatening illness that requires prompt and appropriate treatment.
- Drugs and any other substances suspected of provoking the attack should be withdrawn, symptoms relieved using drugs known to be safe in acute porphyria and calorie intake maintained.
- Intravenous haem arginate should replace carbohydrate loading for the specific treatment of severe acute attacks.
- Haem arginate should be given as soon as the diagnosis is established, preferably within 48 hours of onset of symptoms; it will not reverse a developing or established neuropathy.
- There is increasing evidence that haem arginate is safe, decreases analgesic requirements, shortens length of stay in hospital and lessens the risk of serious complications, such as peripheral neuropathy.