



CARDIFF AND VALE NHS TRUST  
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# PORPHYRIA

## A Medicines Information Bulletin



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## Acknowledgements

This information is issued on the understanding that it is the best available from the resources at our disposal at the date of preparation and does not necessarily reflect district or hospital policies. Manufacturers' Summaries of Product Characteristics should be consulted for full prescribing information.

The bulletin is primarily aimed at healthcare professionals, for example Doctors and Pharmacists throughout the United Kingdom.

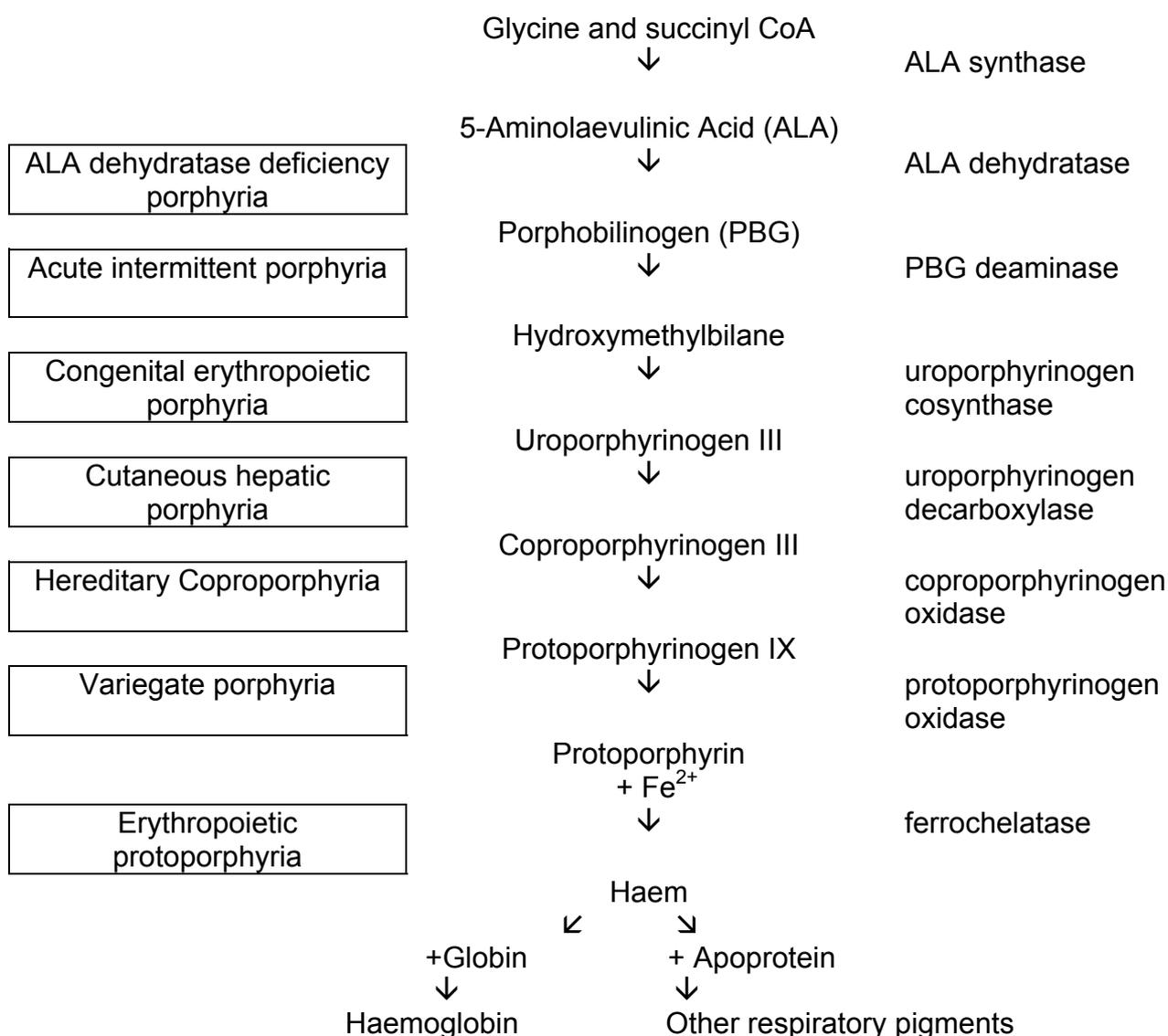
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Thanks to Dr Mike Badminton, Director, SAS Porphyria service, Department of Medical Biochemistry & Immunology, University Hospital of Wales, for his specialist advice during the compilation of this bulletin.

## WHAT IS PORPHYRIA?

The porphyrias are a heterogeneous group of metabolic disorders arising from defects in the haem biosynthetic pathway. Each porphyria is characterised by a specific partial enzyme deficiency (fig 1). This leads to altered patterns of synthesis of porphyrins and their precursors, which accumulate and are linked to clinical manifestations.<sup>1,2</sup> The majority of the body's haem is produced in erythroid cells and the liver.<sup>2</sup> The rate of synthesis of the first intermediate in the pathway, 5-aminolaevulinic acid (ALA), is important in controlling the formation of haem.<sup>1</sup> In the liver, the synthesis of ALA by ALA synthase is increased by increased demand for haem<sup>3</sup> and, in turn, repressed by haem.<sup>2</sup> Control of haem synthesis in the erythroid cells is more complex and ALA synthase is not repressed by haem.<sup>1</sup> Clinically porphyria can present with acute neurovisceral symptoms, skin lesions or both, depending on the specific enzyme deficiency.<sup>3</sup>

**Fig. 1 Haem biosynthesis and porphyria**



There are two main groups of porphyrias:-

- (1) The Acute porphyrias
- (2) The Non-Acute porphyrias

## ACUTE PORPHYRIAS

### Types of acute porphyria

- ALA DEHYDRATASE DEFICIENCY PORPHYRIA (ADP)
- ACUTE INTERMITTENT PORPHYRIA (AIP)
- VARIEGATE PORPHYRIA (VP)
- HEREDITARY COPROPORPHYRIA (HCP)

All these types of acute porphyria share presentations which may include, attacks of abdominal pain, limb weakness and various neuropsychiatric features. In addition, variegate porphyria and hereditary coproporphyria demonstrate photosensitive skin changes.<sup>2-4</sup>

All the acute porphyrias, with the exception of ALA dehydratase deficiency porphyria (ADP) are inherited as an autosomal dominant trait. ADP is inherited as an autosomal recessive condition.<sup>4</sup> ADP is very rare and only six cases have been reported (none in the United Kingdom),<sup>5</sup> and it will not be discussed further.

The exact prevalence of acute porphyrias is difficult to determine. Clinically overt cases are rare. However, it is well known that the clinical penetrance of the disease is low, with 80 to 90% of carriers of the relevant gene defects remaining asymptomatic.<sup>3,4,6</sup> A study in healthy French blood donors assessed the prevalence of the gene mutation for AIP to be 1:1675.<sup>7</sup> In most European countries it is estimated that 1-2 per 100,000 of the general population experience an acute porphyria attack.<sup>4</sup> The prevalence of the type of acute porphyria also varies in certain populations. In Europe AIP is the most common form with Northern Sweden having the highest prevalence of between 60 to 100 per 100,000 population.<sup>1</sup> Variegate porphyria is about a third less common,<sup>3</sup> except among the Afrikaner population in South Africa, where the estimated prevalence is between 1 per 250 and 1 per 500 population.<sup>8</sup> Hereditary coproporphyria is the least common of the autosomal dominant acute porphyrias.<sup>3</sup>

In very rare circumstances homozygous forms of each of the acute porphyrias have been described,<sup>2,4</sup> as have simultaneous deficiency of two enzymes of the haem biosynthetic pathway, known as dual porphyrias.<sup>9</sup>

Patients who have never experienced acute attacks are termed latent. Family members of patients with acute porphyrias should be offered screening so that those affected can be advised about avoiding factors which increase the risk of an acute attack.<sup>4,10</sup>

In addition to the enzyme defect, clinical presentation of acute porphyria appears to require additional precipitating factors. These factors may affect the haem

biosynthetic pathway by increasing the demand for haem, by causing further decreases in enzyme activity, or by a combination of these effects.<sup>4</sup>

In the acute porphyrias commonly used drugs can precipitate an acute attack (see later section on drug administration). Updated drug lists of safe and unsafe drugs are an essential reference. However, the precipitating factor is not always clear and several factors may act together to induce an acute porphyria attack. These factors may include, alcohol, endogenous hormone changes, infections, weight loss, calorie restriction, smoking and stress (emotional and physical e.g. due to intercurrent illness).<sup>1,3,5</sup> Undertaking major surgery may pose a particular risk as, unless precautions are taken, several of the above risk factors may be experienced concomitantly. For further information see General anaesthesia in patients with porphyria (page 12).

### **Acute intermittent porphyria**

This is the most common and severe of the acute porphyrias resulting from a deficiency of PBG deaminase, which acts as a second rate-limiting enzyme in the haem biosynthetic pathway.<sup>11</sup> The activity of PBG deaminase is half normal, both in acute and latent cases.<sup>1,5</sup>

As a result of the deficiency in PBG deaminase there may be excess formation and urinary excretion of the porphyrin precursors, ALA and PBG.

Attacks are about five times more common in females than in males.<sup>3,12</sup> The peak occurrence of attacks is in the third and fourth decades, with symptoms being rare before puberty and post menopause.<sup>3</sup>

Clinical penetrance is low and patients may have no family history, the condition having remained latent or unidentified for several generations. The frequency and severity of attacks vary considerably from patient to patient. In a large proportion, the disease remains latent throughout life, even in the presence of precipitating factors. Other patients experience frequent and sometimes life-endangering attacks even in the absence of extrinsic precipitating factors.

### **Variegate porphyria**

Variegate porphyria is less common than AIP. It results from a primary deficiency in the enzyme protoporphyrinogen oxidase, and a secondary deficiency in PBG deaminase.<sup>4,8</sup> Symptomatic variegate porphyria may manifest with skin lesions alone (about 60% cases), acute attacks alone (20% cases) or both (20% cases).<sup>10</sup> Skin lesions, due to photosensitivity, have been reported to affect approximately 40% of gene carriers,<sup>13</sup> and are identical to those seen in porphyria cutanea tarda.<sup>3</sup> Acute attacks tend to be less severe and less frequent than in AIP.<sup>14</sup>

### **Hereditary coproporphyria**

Hereditary coproporphyria is the least common of the autosomal dominant acute porphyrias.<sup>5,10</sup> The primary enzyme deficiency is in coproporphyrinogen oxidase.<sup>8</sup> As with variegate porphyria there is also a secondary deficiency in PBG deaminase.<sup>4</sup> Clinical presentation is with acute attacks only (approximately 75%), or an acute attack accompanied by skin lesions (approximately 20%).<sup>3,15</sup> Occasionally (5-10%

cases) hereditary coproporphria may manifest in skin lesions alone<sup>3</sup> usually in association with hepatobiliary disease.<sup>10</sup>

### **Signs and symptoms of acute porphyria attacks**

Abdominal pain, which is often very severe, is a presenting complaint in the majority of cases.<sup>4,6</sup> It commonly mimics acute abdominal crisis,<sup>2</sup> and requires opiate analgesia for relief.<sup>3</sup> Constipation, nausea, and vomiting are often associated.<sup>2,4,6</sup> Frequently pain in the back or in the extremities is present.<sup>2</sup>

Cardiovascular features, such as hypertension and tachycardia, are also common, occurring in around two thirds of patients.<sup>3</sup> Hypertension may become chronic,<sup>8</sup> and require treatment. Arrhythmias, which are a sign of progressive autonomic neuropathy, may result in sudden death.<sup>2</sup>

Motor neuropathy causing muscle weakness and associated loss of sensation over the trunk and thighs may occur.<sup>3</sup> This can progress to quadriparesis and respiratory failure.<sup>3,8</sup> However, due to prompt treatment, the risk of progressive neuropathy and death is lower now than in the past.<sup>2,3</sup> Misdiagnosis or exposure to additional precipitating factors, for example the administration of unsafe drugs, insufficient carbohydrate intake, or untreated infection increases the risk of death.<sup>2</sup>

Convulsions may occur and may be associated with hyponatraemia, which can occur in up to 40% of acute attacks.<sup>3</sup> Psychiatric changes, such as confusion, disorientation, hallucinations and paranoia may be present during acute attacks. However, little evidence exists for the persistence of long-term psychiatric features during remission, although patients may report increased anxiety between attacks.<sup>3,12</sup>

In an acute attack, passed urine may become dark on standing, due to the conversion of PBG to a brownish-red pigment porphobilin.<sup>5</sup> Non-enzymatic formation of these coloured compounds is promoted by exposure to light, heat and an acid pH.<sup>1</sup> Accurate measurement of urinary PBG is an essential examination in the diagnosis of acute porphyria.<sup>2</sup>

## **MANAGEMENT OF ACUTE ATTACKS**

Patients in acute attacks should have regular monitoring of pulse, blood pressure and respiratory rate. Any drugs used during an acute attack should be safe to use in acute porphyrias.

### **Specific Treatment**

#### **Haem arginate**

Haem arginate replenishes the body's haem stores. Through negative feedback this inhibits ALA synthase, thus reducing the production of porphyrins and their precursors, ALA and PBG.<sup>16</sup>

## Dose

For the treatment of an acute porphyria attack the recommended dose of haem arginate is 3mg/kg (to a maximum of 250mg) once daily for four consecutive days.<sup>17</sup> Some references suggest that, for convenience, 250mg (1 ampoule) for adults may be given irrespective of their weight.<sup>10,18</sup> This would be suitable for patients weighing  $\geq 70$ kg. For patients weighing less than this rounding the dose to the nearest 25mg (1mL) would seem appropriate.

## Administration

The manufacturer recommends that haem arginate should be administered by intravenous infusion over at least 30 minutes in 100mL of sodium chloride 0.9%.<sup>17</sup> Some references recommended a slightly shorter infusion duration of 15-20 minutes.<sup>10,16,18</sup> Haem arginate is irritant to the veins and should be administered through a large vein in the forearm or via a central line.<sup>17</sup> After infusion the vein should be flushed well with 100mL of sodium chloride 0.9%, initially as three or four 10mL boluses and then the remaining volume may be infused over 10-15 minutes.<sup>17</sup> It is also recommended that the arms are alternated each day to limit local perivenous inflammation.<sup>17</sup>

Because haem arginate is a dark solution, making it difficult to check for absence of particles, it is recommended that it is administered using a 15-20 micron in-line filter.<sup>17,19</sup> This can be done by using an intravenous giving set with an integrated, appropriate sized filter.

The manufacturer also recommends that haem arginate should be diluted with sodium chloride 0.9% in a glass bottle.<sup>17</sup> However, there may be difficulties in obtaining supplies of this. Therefore, a pragmatic approach, to avoid delaying emergency treatment, would be to use plastic containers ensuring preparation occurs immediately prior to administration (unlicensed use).

Haem arginate is irritant to the veins and may cause thrombophlebitis. Repetitive peripheral use may lead to the loss of the superficial venous system and the consequent need for a central line. Central lines may also, in time, become obstructed with haem deposits. Although unlicensed and lacking robust evidence, experience suggests that administration of haem arginate in 100mL human albumin helps reduce these problems,<sup>10</sup> and this has become accepted practice in several countries (e.g. South Africa and France). There currently appears to be no formal consensus on what strength of human albumin to use and between 4 and 20% have been used.<sup>10</sup> However, as each molecule of albumin has a single high affinity haem binding site, theoretically a 1:1 molar ratio of albumin to haem is suggested to ensure binding of all haem molecules.<sup>20</sup> Using albumin 20%, as in South Africa,<sup>14</sup> would appear logical as this will provide closest to a 1:1 ratio. The maximum recommended rate of infusion of human albumin 20% solution is 2mL per minute.<sup>21</sup> Therefore, the rate of haem arginate administration may need to be altered to take this into account. As a pragmatic approach, administering the dose in 100mL of human albumin 20% over 60 minutes would appear reasonable. Because human albumin 20% is hyperosmotic, adequate hydration should be maintained and electrolytes monitored.<sup>21</sup>

## Prophylactic use

In individuals who suffer recurrent acute attacks, especially women suffering cyclical attacks, early administration of haem arginate for one or two doses may abort the development of an attack without the need for a full course. Following consultation with an expert porphyria centre, haem arginate may also sometimes be used prophylactically as a single dose once or twice a week to help with difficult disease control.<sup>18</sup>

## Availability

Haem arginate (Normosang<sup>®</sup>) is available from Orphan Europe during office hours and out of hours is available from:

- St Thomas' Hospital, Lambeth Palace Road, London (see BNF for details)

## Supportive Treatment

Refer to table 1 (page 8) and additional information below.

## Removal of precipitating factors

Any drugs not known to be safe in the acute porphyrias should be discontinued. Other potential risk factors, such as infection, should be treated.<sup>16</sup>

## Nutrition

Impaired nutrition may aggravate an acute porphyria attack. Therefore, it is crucial that adequate calories are given. This should preferably be orally or, if necessary, nasogastrically as carbohydrate rich supplements. If enteral administration is not possible, e.g. due to vomiting, glucose should be administered intravenously.<sup>18</sup> Hypotonic glucose in water infusions, such as glucose 5%, should be avoided as these may aggravate hyponatraemia. At the University Hospital of Wales the local expert recommends two litres per 24 hours of sodium chloride 0.9% with 10% glucose.<sup>22</sup> This will provide 200g of glucose per day. However, if this is unavailable sodium chloride 0.9% with 5% glucose may be used.<sup>22</sup>

## Pain

Opiates are invariably required to control the severe pain associated with acute porphyria attacks. Simple analgesics such as aspirin, paracetamol and codeine are usually ineffective.<sup>18</sup> Because porphyria attacks are usually short-lived and infrequent, the risk of dependence on opiates is low.<sup>18</sup> However, every attempt should be made to withdraw these drugs between attacks. As high doses of opiates tend to be required, a suitable antiemetic should be used.<sup>3</sup> Adding chlorpromazine or promazine, which will help with nausea, anxiety and restlessness, may also help reduce the analgesic requirements.<sup>3,18</sup>

## Hypertension and/or tachycardia

These can be controlled with beta-blockers, such as propranolol, labetalol or atenolol.<sup>3</sup>

## **Neurosis or psychosis**

These symptoms require sedatives or tranquillisers, e.g. lorazepam,<sup>2</sup> and/or chlorpromazine or promazine.<sup>3,18</sup>

## **Seizures**

As most anticonvulsants are porphyrinogenic, they should be avoided and intravenous lorazepam or clonazepam should be used to treat seizures in the acute presentation.<sup>22</sup>

## **Constipation**

This requires regular laxatives e.g. bulk laxatives, senna or lactulose.<sup>2,3,18</sup>

## **Nausea and vomiting**

These symptoms require a suitable antiemetic, such as prochlorperazine, promazine or chlorpromazine.<sup>2,18</sup>

## **Skin photosensitivity (in variegate and hereditary coproporphria)**

No specific treatment exists. The management mainly consists of measures to protect fragile skin and avoidance of sunlight.<sup>2,3</sup>

Conventional sunscreens are not effective in preventing photosensitivity reactions in porphyria. This is because they filter out the shorter wavelength UVB light responsible for sunburn.<sup>16</sup> Porphyrins are activated by long UVA wavelengths (400-410 nm) and some visible light wavelengths.<sup>16,22</sup> Newer high-protection factor sunblocks containing micronised titanium dioxide may be an acceptable compromise.<sup>16</sup> However, opaque sunblocks containing high concentrations of zinc oxide or titanium dioxide are the most effective and three tinted versions (coral, beige and coffee) of a specially formulated product are available in the United Kingdom (Tayside Pharmaceuticals, Ninewells, Dundee).<sup>22</sup> Appropriate clothing to block the sun is also important and can be more effective than creams and lotions.<sup>16</sup>

**Table 1 - Drug Treatments in Acute Porphyria**Symptomatic treatment

<b>Condition</b>	<b>Drug Category</b>	<b>Drug*</b>
Abdominal Pain	Analgesics	Aspirin Diamorphine Dihydrocodeine Ibuprofen Morphine Paracetamol Pethidine
Vomiting	Anti-emetics	Chlorpromazine Ondansetron Prochlorperazine Promazine
Hypertension and tachycardia	Antihypertensives	Beta-blockers e.g: Atenolol Labetalol Propranolol
Neurosis, psychosis and seizures	Sedatives, tranquillisers and anticonvulsants	Chlorpromazine Clonazepam Lorazepam Promazine
Constipation	Laxatives	Bulk-forming (ispaghula) Lactulose Senna

**\* Drugs are listed alphabetically rather than preferred order of treatment. Management of symptoms should be individualised to meet the needs of the patient.**

## PREVENTION OF ACUTE ATTACKS (including advice to patients)

Acute attacks are commonly precipitated by factors which increase demand for haem in the liver. Events which may precipitate this do so by increasing the activity of ALA synthetase and stimulating the production of haem precursors (PBG and ALA).<sup>8</sup>

A number of factors can cause acute exacerbations and patients should be counselled about them, including:-<sup>8</sup>

- Physiological hormone fluctuations e.g. menstrual cycle
- Fasting/dieting (if weight loss is required the advice of a dietician should be sought)
- Stress
- Infection
- Alcohol should be restricted and smoking discouraged. If avoiding alcohol is impossible then intake should be kept as low as possible avoiding heavy red wine, brandy and liqueurs.<sup>10</sup> "Binge" drinking is particularly dangerous.

### **Screening of families**

Relatives of affected patients should be offered screening for acute porphyrias. This can be undertaken at any age. Children should be tested before puberty and testing with parental consent is therefore considered ethical.<sup>22</sup>

Measurement of metabolites or enzyme activities has major limitations, and has largely been replaced by genetic testing. This requires the mutation carried by the affected family member to be identified first. Formal family studies and genetic counselling are best undertaken in collaboration with a clinical genetics centre.<sup>22</sup>

Even though acute attacks are very rare before puberty, presentation has occurred and affected children should still avoid all those drugs that are not known to be safe in porphyria.<sup>10</sup>

## DRUG ADMINISTRATION IN PATIENTS WITH ACUTE PORPHYRIA

There are a number of potential pathways by which agents are likely to be porphyrinogenic making it difficult to predict which drugs are safe or unsafe.

Most of the pathways however involve an increased demand for haem by increasing utilisation or by reducing the level of haem production. The former mechanism would involve increased demand for oxidative processes mediated through the cytochromes e.g. drugs which increase the synthesis of cytochrome P450 enzymes in the liver also increase the synthesis of haem. When the liver in a patient with acute porphyria is induced to make more haem precursors, an exacerbation of porphyria can follow.

Fortunately many drugs do not increase the synthesis of cytochrome P450 enzymes and are therefore likely to be safer in porphyria.

However, a drug which does not induce cytochrome P450 enzymes and haem synthesis in the liver may worsen porphyria through other mechanisms. Unfortunately, these mechanisms have been little studied and are not well understood.

Before a prescription is written or medication administered to a patient with acute porphyria the safety of that drug should be checked on lists of safe medicines such as the one produced by the Welsh Medicines Information Centre in Cardiff. The centre has expertise in this area of medicines safety in the porphyrias and the centre is supported by the SAS Porphyria Service in the Department of Medical Biochemistry & Immunology, whose current Director is Dr Mike Badminton. The Welsh Medicines Information Centre can be contacted for further information and advice on the safety of drugs in porphyria. See pages 17-19 for further details.

Anecdotal experience of the use of medicines in patients with porphyria is one way of labelling a medicine as safe or unsafe. Alternatively cell culture and animal models can be used to ascertain whether a drug may be likely to be porphyrinogenic. Both cell culture and animal models tend to overestimate the porphyrinogenicity of drugs.

A three year European Porphyria Network public health project is underway (since May 2007) whereby clinical data on drug use will be obtained from patients with an acute porphyria by four co-ordinating centres, including the Welsh Medicines Information Centre. The aim is to collect 4000 high quality and reliable reports of clinical experience of drug use in these individuals. It is envisaged that this information once available will inform decision making and allow experts to provide better advice regarding the safety of medicines in porphyria.

### **Prescribing for patients with acute porphyria**

Prescribing for patients with non-acute porphyria is discussed on page 16.

## **General advice**

In acute porphyria, where possible, SAFE drugs should be selected. However, if an unsafe drug needs to be used, for example, where no alternative exists or in a life threatening illness, the drugs may be administered with caution.

Unsafe drugs should be administered under close supervision with measurements of urinary porphobilinogen (PBG) before and every 2-3 days after giving the drug. If PBG excretion increases, the drug should be stopped.

A “pitfall” in evaluating PBG levels is that not all biochemistry laboratories have the capability to monitor it. Also some patients have naturally high levels of PBG without any link with drug administration.

## **Selecting a drug**

- **Always select the safest alternative**  
For example there is little justification for prescribing erythromycin or a tetracycline if a penicillin would work just as well.
- **Where there is no alternative**  
Firstly, it is worth confirming that the diagnosis of acute porphyria is robust. Some patients may have been informed that they have porphyria based on equivocal investigations performed many years ago or due to misinterpretation of porphyrin measurements. If there is any doubt, it may be possible to arrange retesting. Should they not have acute porphyria prescribing becomes easier (see section on porphyria cutanea tarda and erythropoietic protoporphyria pages 15-16).

Where porphyria is confirmed, or it is not possible to exclude the diagnosis, one must make a risk-benefit decision. Is the expected result from the drug therapy sufficiently important to the patient’s health to risk an acute attack? If not, refrain from prescribing. If so, the following is recommended:-

- Select the safest drug.
- Warn the patient that the drug you are prescribing cannot be guaranteed safe and obtain their consent to use it.
- Advise patient to stop the drug immediately and seek medical advice should they develop severe abdominal pain or darkening of the urine.
- In particularly problematic cases or when there is a strong clinical indication for a drug which is regarded as unsafe, such as tuberculosis, epilepsy, cancer or HIV you may wish to consider contacting the Welsh Medicines Information Centre for advice.
- Consider measuring urinary PBG levels before and during treatment, if they rise significantly the drug should be stopped.

The Welsh Medicines Information Centre can be contacted for further information and advice on selecting drugs for individuals with acute porphyria. See pages 17-19 for details.

## **General anaesthesia in patients with acute porphyria**

General anaesthesia poses the greatest risk to patients whose porphyria is or has been recently active. However, general anaesthesia may be undertaken safely providing appropriate safe drug choices are made for the procedure.<sup>10</sup> See [www.porphyrria-europe.org](http://www.porphyrria-europe.org) for information on anaesthetic medication choices in acute porphyria.

In addition to safe drug choices for the anaesthesia itself, consideration should be given to the following to avoid provoking acute attacks:-

- Ensure effective pre and post-operative analgesia to minimise stress and pain from procedure.<sup>10</sup>
- Ensure any resulting infection(s) are treated aggressively to avoid post-operative porphyria complications.<sup>10</sup>
- Ensure patients avoid a pre and post-operative starvation (this can be avoided by ensuring the patient receives intravenous glucose infusions until able to resume an adequate diet).<sup>10,23</sup>

## **Travelling with porphyria**

### **Acute Porphyrias**

The Welsh Medicines Information Centre is often asked about the safety of travel vaccines and malaria prophylaxis for international travel in patients with porphyria.

In general travel vaccines are considered safe in the acute porphyrias. However, there has been an unpublished report of an acute porphyria attack following yellow fever vaccination and therefore, caution may be warranted when administering live vaccines. Consider contacting the Welsh Medicines Information Centre for further information or advice. The following antimalarials are suitable for use:-<sup>24</sup>

- Chloroquine
- Malarone<sup>®</sup> (atovaquone and proguanil)
- Mefloquine
- Proguanil

Factors which may be involved in the provocation of an acute attack include starvation, alcohol, infection, stress and hormonal changes, for example in the premenstrual period. One reference suggests that many of these factors were implicated in causing acute attacks in five reported cases after international air travel.<sup>25</sup>

To minimise the risks of experiencing an acute attack, porphyria sufferers should be advised to avoid alcohol whilst flying and to maintain adequate hydration by drinking plenty of non-alcoholic fluids. They should be advised not to miss meals and to consume meals with high carbohydrate content.

Travellers with an acute porphyria should consider the healthcare facilities in the country to which they are travelling.

## Non-acute porphyrias and antimalarials

Chloroquine is the only antimalarial to be avoided in porphyria cutanea tarda, a non-acute porphyria. No medicines are considered 'unsafe' in the other forms of non-acute porphyria. See also page 16 (Prescribing in the non-acute porphyrias).

## Female patients with acute porphyria: additional considerations

Women are five times more likely than men to experience an acute porphyria attack.<sup>3</sup> Endogenous hormones, particularly progesterone are important precipitants of acute attacks, which may partially explain this increased incidence and why attacks are more common during the luteal phase of the menstrual cycle.<sup>26</sup>

Women who experience frequent cyclical attacks confined to the luteal phase can, in consultation with a porphyria specialist, be treated with gonadotrophin-releasing hormone analogues e.g. goserelin or buserelin, which induces a chemical menopause, and in some cases will halt acute attacks.<sup>12</sup>

## Gonadotropin-releasing hormone analogues

Therapy should be started within the ten days after the start of a menstrual period to minimise the associated hormone surge which can cause an acute attack. Depot preparations are the most effective as they reduce the risk of missed doses, hormone surge and recurrent acute attack. Using low-dose oestrogen, e.g. Premarin<sup>®</sup> 0.3mg,<sup>16</sup> can prevent menopausal symptoms and a decline in bone mass but is not without risk. It is recommended that gynaecological examinations and bone density determinations should be carried out every six months during treatment.<sup>16,26</sup> In patients with an intact uterus, unopposed oestrogens are not favoured because of the risk of endometrial hyperplasia and possible neoplastic transformation. It is therefore recommended that if supplemental oestrogen is started the patient should be considered for endometrial curettage at six-monthly intervals. Treatment with a gonadotropin-releasing hormone analogue should be continued for at least 18 months.<sup>16</sup>

## Pregnancy

Although pregnancy results in an increased level of progesterone it is well tolerated in most women<sup>26</sup> and does not appear to be a major risk to the patient with porphyria.<sup>8</sup> However patients with recurrent acute attacks are usually advised to avoid pregnancy until their disease enters a latent phase. Several of the possible complications during pregnancy are related to the labour and administration of unsafe drugs, e.g. ergometrine and some anaesthetic agents<sup>8,16</sup> and/or inadequate nutrition<sup>22</sup> which may increase the risk of an acute attack. Where acute attacks do occur standard treatment with haem arginate is advised. Experience of expert porphyria centres in the United Kingdom, France and South Africa indicates that haem arginate is safe during pregnancy.<sup>16,22</sup>

## Hormonal contraception

The contraceptive pill, particularly the progestogen component, can provoke acute attacks in patients with acute porphyria and non-hormonal methods of contraception e.g. intrauterine contraceptive devices\*, condoms, diaphragm, spermicidal jellies and male or female sterilisation should be preferred.<sup>10,16</sup> →

Women who have previously had an acute attack or suffer from acute intermittent porphyria or those with high urinary PBG excretion levels are at particularly increased risk of suffering an acute attack due to hormonal contraception.

\*Some intrauterine devices are progesterone based, despite this, only a small amount is absorbed, and so the risk of provoking an acute attack is likely to be small. Further advice can be sought from the Welsh Medicines Information Centre.

### Hormone replacement therapy (HRT)

According to experts in South Africa there is evidence that progestogens are more dangerous than oestrogens. If hormone replacement is necessary wherever possible an oestrogen-only preparation should be considered. However, unopposed oestrogen use in a woman with an intact uterus may predispose her to endometrial carcinoma. This risk needs to be carefully weighed against the potential risk of an acute porphyria attack resulting from the addition of a progestogen.<sup>16</sup>

## **NON-ACUTE PORPHYRIAS OR CUTANEOUS PORPHYRIA**

### Types of non-acute porphyria

- CONGENITAL ERYTHROPOIETIC PORPHYRIA (CEP)
- PORPHYRIA CUTANEA TARDA (PCT)
- ERYTHROPOIETIC PROTOPORPHYRIA (EPP)

In all the cutaneous porphyrias, porphyrins (which are photosensitising) are deposited in the upper epidermal layer and these are responsible for the characteristic skin lesions.

### Congenital erythropoietic porphyria

CEP, otherwise known as Gunther's disease is fortunately very rare. Both sexes are equally affected and patients present with severe photosensitivity, usually within the first few months of life.<sup>27</sup> As a result of the photosensitivity they experience profound skin fragility which presents as blisters, erosions and scarring in sun-exposed areas.<sup>28</sup> These can progress to deformities and mutilations particularly on the face, hands and scalp, additionally they may develop secondary infections. Patients may also experience pigment alterations, ocular scarring, erythrodontia (red stained teeth) due to the porphyrin content and facial hypertrichosis.<sup>27,28</sup> Haemolysis is common, leading to anaemia and secondary splenomegaly.<sup>27</sup>

### Management

#### Supportive<sup>27,28</sup>

- Avoiding sun exposure
- Oral administration of charcoal and colestyramine (to absorb porphyrins)
- Blood transfusion

- Splenectomy (to reduce risk of haemolytic anaemia)
- Bone marrow suppression with hydroxyurea (to inhibit erythropoiesis)

### Definitive

- Allogenic bone marrow transplantation<sup>29</sup>

### **Porphyria cutanea tarda or cutaneous hepatic porphyria**

PCT is the most common cutaneous porphyria with an estimated incidence of 1 in 10,000 (which varies between countries).<sup>30</sup>

In PCT a deficiency in hepatic uroporphyrinogen decarboxylase results in the accumulation of large amounts of photoactive porphyrins<sup>16</sup> which are released into the circulation.<sup>22</sup> It can be an inherited or more commonly an acquired disease and is manifested as skin fragility and blisters in light-exposed areas,<sup>30</sup> erosions, scarring alopecia, pigmentary changes<sup>28</sup> and hypertrichosis.<sup>30</sup> Liver disease including hepatocellular carcinoma is common.<sup>28,30</sup>

Known precipitants for PCT include alcohol, oestrogen-containing medication, viral infections (hepatitis C, HIV), chemical toxicity and other systemic disorders e.g. systemic lupus erythematosus and lymphoma.<sup>16</sup>

Almost all patients have increased stainable iron in the liver.<sup>30</sup>

### Management<sup>30</sup>

- Elimination of the underlying cause e.g.
  - Abstaining from alcohol.
  - Stopping oestrogen therapy
- Sun avoidance
- Venesection to remove excess iron (usually achieved by two-weekly venesection of 500ml blood).
- Chloroquine therapy at a dose of 125mg-250mg twice a week has been shown to improve symptoms of blisters and fragility within six months. It is normal for urine to be red during treatment with chloroquine due to the presence of porphyrins in the urine. Introduction of therapy is also frequently associated with a temporary aggravation of skin disease which resolves as the disease comes into remission.<sup>16</sup> Higher doses e.g. antimalarial doses can cause a dangerous reaction in PCT patients after a few days with pyrexia and acute hepatitis.<sup>30</sup> Hydroxychloroquine 100mg-200mg twice weekly has also been used but the remission is shorter than with chloroquine. These agents work by complexing with porphyrins and promoting their excretion into bile.<sup>22,30</sup>

### **Erythropoietic protoporphyria**

EPP is the second most common type of porphyria and usually presents in early childhood with painful photosensitivity. The disease manifests itself with urticarial lesions, oedema and sometimes painful petechiae.<sup>28</sup> Chronic changes include linear scarring and waxy thickening of the skin.<sup>3</sup> Systemic complications maybe present such as anaemia, cholelithiasis, and liver dysfunction,<sup>28</sup> which may rarely result in hepatic failure.<sup>3</sup>

→

## Management

- Avoidance of sun<sup>3</sup>
- Narrow band UVB therapy<sup>22</sup>
- Sunblocks containing zinc oxide and/or titanium dioxide (e.g. Dundee Sun Screen, Tayside Pharmaceuticals, Dundee).<sup>22</sup> See also page 7 (Skin photosensitivity in variegate and hereditary coproporphyria).
- Oral beta carotene is advocated to increase sunlight tolerance,<sup>16</sup> in doses of 120-300mg per day in divided doses.<sup>31</sup> Monitoring is recommended to ensure adequate plasma levels are reached (11-15 micromoles/L).<sup>3,22</sup> These levels cause a yellow/orange discolouration of the skin that may be considered an undesirable effect. A 30mg capsule can be imported into the United Kingdom through IDIS (an importation company) as a suitable licensed preparation is not available in the United Kingdom. If there is no increase in sunlight tolerance after three months of optimum beta carotene plasma levels, treatment has failed and should be stopped.<sup>3</sup>
- When liver dysfunction is present measures taken to reduce plasma protoporphyrin levels include colestyramine<sup>3,28</sup> and chenodeoxycholic acid,<sup>28</sup> activated charcoal<sup>3,16</sup> and hyper-transfusion.<sup>22</sup> Ultimately liver transplantation may be required in some cases.<sup>28</sup>

## Prescribing in non-acute porphyrias

Porphyria cutanea tarda, erythropoietic protoporphyria and congenital erythropoietic porphyria are non-acute porphyrias.

If patients have unequivocally been diagnosed as having **erythropoietic protoporphyria** or **congenital erythropoietic porphyria** there are thought to be **NO UNSAFE DRUGS** since acute attacks are not encountered.<sup>16</sup>

For patients diagnosed with **porphyria cutanea tarda** all drugs are **SAFE** except:

- Chloroquine and related drugs in antimalarial doses for both treatment and prophylaxis.<sup>1,16</sup>

**N.B.** low dose chloroquine 125mg to 250mg twice a week is often used to treat porphyria cutanea tarda. Higher doses can cause rapid mobilisation of porphyrins from the liver<sup>22</sup> which may lead to acute hepatitis.<sup>30</sup>

- Oestrogens (natural and synthetic) may provoke symptoms (skin lesions) and should not be prescribed until the disease has been brought into remission.<sup>16</sup>

**N.B.** It is generally recommended that where oestrogen therapy is deemed a provoking factor it is withdrawn until remission is achieved. Clinical experience suggests that therapy can then be safely reintroduced although patients should be followed up annually.<sup>22</sup>

## WELSH MEDICINES INFORMATION CENTRE

The Welsh Medicines Information Centre (WMIC) at the University Hospital of Wales in Cardiff has provided information about the use of drugs in porphyria since September 1995.

The service is provided in conjunction with Dr Mike Badminton, Senior Lecturer and honorary consultant in medical biochemistry. Dr Badminton is the director of the Cardiff SAS Porphyria Service, which provides a diagnostic and clinical advisory service for all types of porphyria ([www.cardiff-porphyria.org](http://www.cardiff-porphyria.org)).

A number of lists of drugs that are classified as safe or unsafe in the acute porphyrias have been produced. The Welsh Medicines Information Centre produces a list of drugs considered safe in the acute porphyrias which is updated annually. The list can be located at [www.wmic.wales.nhs.uk/pdfs/porphyria/porphyriasafelist.pdf](http://www.wmic.wales.nhs.uk/pdfs/porphyria/porphyriasafelist.pdf). This list forms the basis for the list of safe drugs on the European Porphyria Initiative website, [www.porphyria-europe.org](http://www.porphyria-europe.org). This European site also has a list of drugs that have been found to be unsafe in individuals with acute porphyria. However there are many drugs for which the safety is largely uncertain.

Recently, a Scandinavian team set up a new database, [www.drugs-porphyria.org](http://www.drugs-porphyria.org), which classifies drugs using a five point classification scale:-

Not porphyrinogenic  
Probably not porphyrinogenic  
Possibly porphyrinogenic  
Probably porphyrinogenic  
Porphyrinogenic

This database has collated information from other drug lists, literature reports and clinical experience along with pharmacokinetic information.

The European Porphyria Initiative website also contains useful information on common prescribing problems.

For further information and advice on the safety of medicines in porphyria the Welsh Medicines Information Centre can be contacted by:-

Telephone: 029 2074 3877  
Fax: 029 2074 3879  
Email: [welshmedicines.information@cardiffandvale.wales.nhs.uk](mailto:welshmedicines.information@cardiffandvale.wales.nhs.uk)

## **Required information for enquiry answering**

Enquirers calling the Welsh Medicines Information Centre for advice regarding the safety of drugs in porphyria should have the following information to offer the centre:-

- Type of porphyria
- Nature of illness e.g. latent or active i.e. number and frequency of attacks
- Whether patient has suffered any drug-induced attacks in the past
- Age of the patient
- Sex of the patient
- Name of the patient

### Type of porphyria

If the type of porphyria is unknown, the centre will assume it is one of the acute forms i.e. the worst case scenario. In this situation it may be unnecessarily recommended that certain drugs are avoided.

### Nature of the illness/Drug-induced attacks

Among individuals with acute porphyria the response to drugs is highly variable.<sup>10</sup> It is possible for an individual with an acute porphyria to tolerate an unsafe drug without adverse effect. This is understandable as multiple factors can be involved with precipitating an acute attack including hormonal changes, stress, infection, reduced calorie intake, alcohol and smoking.<sup>3,5</sup> Thus, administration of a potentially unsafe drug on its own may not be sufficient to precipitate an acute attack, but if other risk factors or additional unsafe drugs are encountered an acute attack may ensue.

Individuals with “latent” porphyria who have never suffered an acute attack may be less likely to have an attack due to an unsafe drug than individuals who have experienced frequent attacks, especially if any of these have been drug-induced.

The fact that a patient with acute porphyria has tolerated a drug without adverse effect does not always mean that the drug will not induce attacks in others. On the other hand, an attack that develops in a patient who is taking a certain drug does not necessarily mean that the drug was the causative agent. A safe drug can be an “innocent bystander” and be falsely blamed for precipitating an attack.

It may be difficult to recognise if a drug is causing an exacerbation of acute porphyria because the symptoms may be delayed and develop slowly. Also, if an individual is taking multiple medicines it may be difficult to appreciate the effects of any one of them.

Reports of suspected drug-induced acute porphyria attacks are of value as they increase our knowledge of drug use in the acute porphyrias, which is still somewhat limited.

The Welsh Medicines Information Centre is currently participating in a three year (started May 2007) European Porphyria Network public health project. The aim of this project is to obtain 4000 high quality and reliable reports of clinical experience of drug use, safely or otherwise, by individuals with an acute porphyria. The project involves collecting information directly from individuals who have an acute porphyria, by way of telephone interviews with the project pharmacist. Anyone wishing to contribute to the project or wanting further information can contact the project pharmacist on 029 2074 4861.

### Age and sex

The age and sex of a patient with acute porphyria are relevant since acute attacks are more common in females especially when they are in their 20s or 30s.<sup>3</sup>

### Name

If the patient's name is known but other details are not, the Medical Biochemistry Department at the University Hospital of Wales can often provide useful information to the WMIC regarding the patient's disease state.

## **SELF-HELP GROUPS**

Newly diagnosed patients understandably may require information about their disease state. Support and advice can be provided by the British Porphyria Association. They can be contacted at:-

British Porphyria Association  
136 Devonshire Road  
Durham City  
DH1 2BL  
Helpline tel: 01474 369231  
Email: [helpline@porphyria.org.uk](mailto:helpline@porphyria.org.uk)  
Website: [www.porphyria.org.uk](http://www.porphyria.org.uk)

## **WARNING JEWELLERY**

It is advised that people with porphyria wear a wrist bracelet or neck pendant that warns they have porphyria. Details of warning jewellery can be obtained from the Medic Alert Foundation:-

1 Bridge Wharf  
156 Caledonian Road  
London  
N1 9UU  
Freephone: 0800 581420  
Tel: 020 7833 3034  
Fax: 020 7278 0647  
Website: [www.medicalert.co.uk](http://www.medicalert.co.uk)

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## GLOSSARY

ADP	5-Aminolaevulinic acid dehydratase deficiency porphyria. A very rare type of acute porphyria.
AIP	Acute intermittent porphyria. An acute porphyria.
ALA	5-Aminolaevulinic acid. The porphyrin precursor produced in the first step of the haem biosynthetic pathway.
CEP	Congenital erythropoietic porphyria. A non-acute/cutaneous porphyria.
EPP	Erythropoietic protoporphyria. A non-acute/cutaneous porphyria.
HCP	Hereditary coproporphyria. An acute porphyria.
PBG	Porphobilinogen. The porphyrin precursor produced in the second step of haem biosynthetic pathway. Levels in the urine are raised during an acute porphyria attack.
PCT	Porphyria cutanea tarda. Non-acute/cutaneous porphyria.
VP	Variegate porphyria. An acute porphyria.

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