Practical considerations in the peri-operative management of patients with acute hepatic porphyria

Journal:	*BJA Education*
Manuscript ID	BJAED-2020-019.R3
Article Type:	Invited Review
Date Submitted by the Author:	19-Sep-2020
Complete List of Authors:	Wilson-Baig , Noamaan; Manchester University NHS Foundation Trust, Anaesthesia and Critical Care Badminton, Michael; University of Wales Cardiff, National Acute Porphyria Service, Medical Biochemistry and Immunology Schulenburg-Brand, Danja; University of Wales Cardiff, National Acute Porphyria Service, Medical Biochemistry and Immunology
Mesh keywords:	Porphyrias, hepatic, anaesthesia, Perioperative Care, Perioperative Medicine

Acute hepatic porphyria and anaesthesia: a practical approach to the prevention and management of acute neurovisceral attacks

N. Wilson-Baig[1,2,*], M. Badminton[3,4] and D. Schulenburg-Brand[4]

[1] Manchester University NHS Foundation Trust, Manchester, UK

[2] Lancaster University, Lancaster, UK

[3] University Hospital of Wales, Cardiff, United Kingdom

[4] University of Wales, Cardiff, Wales, UK

* corresponding author: easinorm@me.com

Keywords: acute hepatic porphyria, acute attack, anaesthetic risks, perioperative

Learning objectives

By reading this article you should be able to:

- Describe the pathophysiology, clinical presentation and management of an acute attack of porphyria, including the appropriate use of haem arginate (HA).
- Discuss the perioperative considerations for managing patients with latent or active porphyria presenting for elective and emergency surgery.
- Know how to access the resources available for expert advice. In the UK, these include the National Acute Porphyria Service (NAPS) and the UK Porphyria Medicines Information Service (UKPMIS).

Key points

- Symptomatic active acute hepatic porphyria (AHP) is rare.
- Anaesthesia can be given safely to patients with a diagnosis of AHP provided that porphyrinogenic medicines, prolonged fasting, dehydration and inadequate analgesia are avoided.
- Acute attacks of porphyria should be managed with advice from a porphyria specialist. In the UK this is provided by the National Acute Porphyria Service (NAPS).
- Haem arginate (HA) treatment is indicated for severe complicated acute attacks or where the episode is not resolving after 12-18 hrs.
- There are no specific risks of anaesthesia associated with the non-acute porphyrias.

Authors' biographies (untitled text box)

Noamaan Wilson-Baig BSc MSc (ClinPharm) MSc (ClinRes) FRCA MRPharmS is an academic specialty registrar in anaesthesia in the North West Deanery.

Professor Michael Badminton PhD, FRCPath is a consultant chemical pathologist at the Cardiff Porphyria Service, and clinical lead for the National Acute Porphyria Service, University Hospital of Wales. He is a board member of the European Porphyria Network, advisor to the British National Formulary, and past associate editor, Annals of Clinical Biochemistry. He is the director of the supraregional porphyria assay service.

Danja Schulenburg-Brand MMed (ChemPath) FRCPath, is a consultant chemical pathologist and clinical lead for the National Acute Porphyria Service Cardiff. She is a member of the British Inherited Metabolic Disease group.

A. Introduction

The porphyrias are a group of mostly inherited conditions resulting from partial deficiency in the activity of enzymes involved in haem synthesis; with the exception of one cutaneous porphyria which is caused by an increase in activity of ALA synthase 2.[1,2] Clinical features depend on the quantity and type of haem biosynthetic intermediates that accumulate (figure 1). Pathway intermediates include aminolaevulinic acid (ALA), porphobilinogen (PBG) and porphyrinogens. The latter are oxidised and excreted as porphyrins. Acute neurovisceral attacks with or without photosensitive skin features characterise the main clinical presentations.[1,2]

Four types of porphyria present with acute attacks.[3] Three are autosomal dominant (AD): acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP). The fourth, an autosomal recessive acute porphyria, 5-aminolevulinate dehydratase deficiency porphyria (ADP) is exceptionally rare and is not discussed further in this article.[3] The non-acute porphyrias, erythropoietic protoporphyria, porphyria cutanea tarda, congenital erythropoietic porphyria and X-linked erythropoietic protoporphyria are not associated with any specific anaesthetic risks.

AIP is the most common acute hepatic porphyria (AHP).[1,3] A recent European study reported that the annual incidence of symptomatic acute porphyria is 0.2 per million (0.13 per million for AIP, 0.08 per million for VP and 0.02 per million for HCP) and the prevalence is 10 per million (1 per 200,000 for AIP).[4] However interrogation of data from genome sequencing projects has identified the prevalence of pathogenic

variants in the *HMBS* gene (causing AIP) to be as high as 1 in 1,782.[5] Penetrance in the general population is therefore approximately 1%, rather than the 10-20% reported in families.[5] Clinicians are therefore more likely to encounter patients with asymptomatic latent porphyria diagnosed through family studies than overtly symptomatic patients with active disease.

Few clinicians have experience in managing symptomatic acute porphyria. This article aims to provide anaesthetists and intensive care physicians with practical advice on managing patients with AHP. We discuss the pathogenesis, precipitating factors, clinical presentation, diagnosis and management of acute neurovisceral attacks. Specific measures to reduce the risk of perioperative acute attacks are also discussed.

A Acute neurovisceral attacks

B Pathogenesis

In each of the autosomal dominant acute porphyrias, there is inheritance of a mutation causing partial deficiency in the respective enzyme activity with consequent accumulation of enzyme substrate. AIP, VP and HCP are caused by partial deficiencies in hydroxymethylbilane synthase, protoporphyrinogen oxidase and coproporphyrinogen oxidase respectively (Figure 1).

Haem supply in hepatic and other non-erythroid cells is regulated by the first enzyme in the pathway, ALA synthase 1 (ALAS1), which is subject to feedback inhibition by haem. An acute attack occurs when hepatic haem requirements are

increased by physiological or environmental precipitants. ALAS1 and the pathway are induced and porphyrin precursors proximal to the deficient enzyme increase. Deficiency of hydroxymethylbilane synthase (HMBS) becomes the rate limiting step in the pathway, resulting in accumulation of the metabolites ALA and PBG (Figure 1). In AIP, the HMBS deficiency is the primary defect, whereas in VP and HCP, HMBS deficiency is understood to be caused by accumulation of the enzyme substrates protoporphyrinogen and coproporphyrinogen (see Fig 1).[6] The excess ALA and PBG are released into the circulation. ALA is understood to be the metabolite most likely to be responsible for the acute neurological dysfunction associated with acute attacks.[7] The regulatory mechanism for hepatic haem synthesis also provides a therapeutic target, as giving exogenous haem can downregulate ALAS1 activity and suppress the excess production of haem precursors.

B Precipitating factors

Precipitants implicated in causing acute attacks include:

- Drugs (prescribed and illicit). Some commonly prescribed medications cause hepatic haem depletion by either induction, or irreversible inhibition of cytochrome P450 enzymes resulting in up regulation of the haem biosynthetic pathway.[8]
- Calorie restriction such as prolonged fasting, diets that exclude carbohydrates, and severe gastrointestinal upset.[2,3] Under fasting conditions the transcriptional coactivator PGC-1α has been shown to act as a nutritional regulator of haem biosynthesis; it upregulates the pathway via induction of ALAS1.[9]

- Fluctuating sex hormone concentration associated with the menstrual cycle, in particular changing progesterone concentrations. Acute attacks are therefore frequently linked to the luteal phase of the menstrual cycle and may be caused by impaired 5α-reduction of steroid hormones.[10]
- Although pregnancy is usually well tolerated, acute attacks have been reported, particularly during the first trimester.[11]
- Excess alcohol consumption, particularly binge drinking, which leads to induction of ALAS.[12]
- Physiological stress including infection.[13]

B Clinical presentation

Most patients with genetically proven but latent acute porphyria remain asymptomatic throughout their lifetime, although they remain at risk of becoming symptomatic when exposed to environmental triggers.[3] The majority of symptomatic patients present between the ages of 15 and 40 yrs and are more likely to be female than male.[4] In general, the older a patient with latent porphyria is, the less likely will be a first acute attack.

The clinical features of acute neurovisceral attacks are identical in all the autosomal dominant acute porphyrias.[3] Symptomatic AIP presents with acute attacks only, whilst in symptomatic HCP and VP photosensitive skin lesions manifesting as fragile skin and blistering in areas exposed to sun can occur during acute attacks or in isolation.[3] Most symptomatic patients have one or a few attacks over a short period

before the disease becomes inactive again. About 5 % of symptomatic AIP patients suffer repeated severe debilitating attacks, but this is rare in VP and HCP.[4,14]

Acute neurovisceral crises relate to the central, peripheral and autonomic nervous systems.[3] In more than 90% of cases, severe diffuse abdominal pain is the main presenting symptom, but back or leg pain may also be a prominent feature. There is usually associated gastrointestinal disturbance including nausea, vomiting and constipation, as well as autonomic features such as hypertension and tachycardia. Cardiac arrhythmias are a rare complication.[1,3,13] Peripheral neuropathy is typically a motor neuropathy affecting distal muscles but mild sensory symptoms such as paraesthesia have also been described.[7] Seizures and psychiatric manifestations such as agitation, depression, insomnia, anxiety, confusion and psychosis are all features of the CNS effects associated with acute attacks. Hyponatraemia is common: it can be severe, develop rapidly and increase the risk of seizures.[3,13] Severe attacks can progress to motor paralysis. This may affect respiratory and pharyngeal muscles and also cause bladder dysfunction.

Patients with a known diagnosis usually have a good understanding of their condition and are often able to recognise the symptoms of an impending acute attack. However other causes such as postoperative complications, pregnancy-related complications or other intra-abdominal pathology should always be excluded, as clinical features are non-specific. Delays in diagnosis and treatment can lead to worse outcomes.

B Laboratory diagnosis

C Diagnosing acute neurovisceral attacks

The porphyrin precursors PBG and ALA are always increased during an acute attack of porphyria.[15] An increased concentration of PBG in a random urine sample collected in a plain universal container without preservatives, confirms an acute attack. As porphyrins and their precursors are sensitive to degradation by light, the urine sample should be protected from light before being sent to the laboratory. In the UK this requires close coordination with the local biochemistry department as testing is not universally available locally. Samples should be tested urgently and so ideally a result should be available within 24 hours of receipt in the laboratory.[16] If qualitative testing is performed, positive results should be confirmed by quantitative testing.[16] Provided the sample is collected during or soon after onset of symptoms, a normal PBG result excludes an acute porphyria attack and should prompt urgent consideration of alternative diagnoses.[16]

Urinary PBG excretion is significantly increased during an acute attack. Analytical methodologies, units and reference intervals differ between laboratories and countries but increases are typically greater than 10 times the upper reference limit.[3] However there is a sustained, sometimes marked, elevation of PBG excretion in between attacks in AIP, which can persist for several years making interpretation difficult.[17] In this context qualitative testing of PBG in known AIP patients with active disease is unhelpful. Interpretation of the urinary PBG concentration requires knowledge of the patient's usual baseline excretion in between attacks and interpretation should be discussed with a porphyria specialist. In contrast, in both VP

and HCP, urine PBG and ALA concentrations return to normal or near normal between acute attacks and therefore urine samples are best collected whilst patients are symptomatic.

C Confirming the type of acute porphyria

Following the biochemical confirmation of an acute attack in a new patient with no family history or previous diagnosis of an AHP, confirmation and identification of the type of acute porphyria should follow. This requires porphyrin analysis of light protected plasma and faecal samples in a specialist laboratory. The plasma porphyrin fluorescence emission wavelength and faecal porphyrin excretion patterns distinguish AIP, VP and HCP (Table 1).[18] All patients who have experienced an acute attack should be referred to a porphyria specialist for follow up.[19] Genetic testing is usually offered to new patients to facilitate cascade testing of relatives at risk. This is generally arranged through referral to clinical genetics.

A. Approach to reduce the risk of acute perioperative neurovisceral attacks

In practice, patients with acute porphyria fall into two distinct clinical subgroups, those with latent AHP, and those with active or recently active AHP. The risk of developing an acute perioperative attack differs between the groups. Patients known to experience repeated acute attacks or who have recently had active disease are at the highest risk of developing symptomatic acute porphyria during the perioperative period.

There has been extensive clinical experience with the use of local anaesthetic agents in patients with acute porphyria. Regional anaesthesia with either neuraxial or peripheral nerve blocks can be used safely in both groups.[20]

B Latent acute porphyria or patients with a family history of AHP

In patients with a known diagnosis of latent acute porphyria, the risk of developing an acute perioperative attack is small, provided the appropriate precautions discussed below are followed. Patients with a family history of AHP requiring urgent anaesthesia, in whom preoperative testing is not possible, should be managed as if they are affected and definitive testing arranged after surgery.

B Active or recently active acute porphyria

Patients with active or recently active acute porphyria are at risk of another episode. As such they would be jointly managed with a porphyria specialist who should be able to provide detailed information about their current clinical status.[19] Acute attacks are unusual after surgery now that barbiturate anaesthesia is rarely used.

B General principles

General anaesthesia may be safely undertaken provided only safe medicines are used (Table 2).[21] If so, having a stock of haem arginate (HA) on site before surgery is rarely required. Perioperative stress should be reduced by effective premedication and pain control. Nausea and vomiting should also be addressed. Table 2 has been compiled using available safety information. It is not an exhaustive list and is intended for guidance only. Some medicines cannot be classified owing to a lack of

safety information (Table 2). UKPMIS can be contacted for advice about specific agents that are not on this list.[21] There is growing popularity for the use of ketamine, especially for induction of anaesthesia in patients who are haemodynamically unstable, and as an alternative analgesic. However, based on the available evidence, ketamine is not considered safe and should be avoided if possible.

The requirement to use 'safe medicines' must be highlighted in the patient's medical record. However, in a life-threatening emergency, no medicine should be withheld if there is no acceptable alternative, even if it is known to be porphyrinogenic.

The partial enzyme deficiencies associated with AHPs do not affect haem synthesis for erythropoiesis. Anaemia is therefore not a feature of the acute porphyrias and should be managed as for any other patient. The risk of allergic reactions in patients with AHP is the same as in the general population and standard management practices should be followed. Thromboprophylaxis should be given as for any patient, using safe anticoagulants when required (Table 2). There are no reports of increased risk of venous thromboembolism in patients with AHP.

Where possible, fasting times for elective procedures should be kept to a minimum by scheduling patients early on theatre lists. As for any patient requiring general anaesthesia for elective procedures, fasting in relation to solid food and particulate liquids should be for at least six hours. Patients should be allowed to drink clear fluids up to two hours before surgery as clear fluids containing carbohydrates

prevent a catabolic state. Urgent procedures should proceed without fasting delay. Fasting intervals for elective procedural sedation should follow local protocols. Although they traditionally are identical to that recommended for elective general anaesthesia, a recent international multidisciplinary consensus statement on fasting before procedural sedation was not in agreement.[22] Each patient and procedure should be stratified for aspiration risk so that a graded fasting period can be recommended.[22]

After surgery, acute porphyria symptoms can be masked by analgesic medicines and mimic complications. Normal eating and drinking should be established before discharge and patients should be given open access to return to hospital if required. If it is not possible to establish postoperative eating and drinking as per usual protocols, i.v. fluids containing glucose, for example, glucose 5% with saline 0.9% or a similar crystalloid, should be continued according to local protocols to limit catabolism until oral intake is established. In patients who are unable to eat and drink for a prolonged period after surgery, advice must be sought from a dietician, and calories provided enterally via the nasogastric route or i.v. as total parental nutrition.

B Specific groups of patients

C Pregnancy

The majority of patients with AHP have normal pregnancies with no clinical issues relating to porphyria.[11] Acute attacks that have occurred during pregnancy have been safely treated with HA without adverse outcomes.[3] However some general

precautions should be taken during labour and delivery. They include avoiding prolonged fasting, use of medicines from the safe drug list and early epidural analgesia to reduce stress. No alteration in epidural drug therapy is required in patients with porphyria. In the presence of features suggestive of porphyria such as seizures, pregnancy-related causes should be excluded. In a clinical emergency, no medicine should be restricted if it is likely to be of clinical benefit in a life-threatening situation. This includes the use of ergometrine.

C Paediatrics

Acute porphyria very seldom manifests before puberty. For asymptomatic children with a known diagnosis of porphyria, as confirmed by family testing, adhering to non-porphyrinogenic medication as a precaution is recommended. There are no other specific requirements, but if concern is expressed by the family then the case should be discussed with a porphyria specialist.[23]

C Patients requiring cardiopulmonary bypass

Case reports mention a theoretical risk of an acute porphyric crisis during cardiopulmonary bypass as a result of stress caused by blood loss, hypothermia and the use of large numbers of medicines required during anaesthesia and surgery.[20,24] However there is currently no evidence that these factors directly precipitate acute attacks. Several reports describe successful surgery in patients requiring cardiopulmonary bypass provided the general measures outlined above are followed.[24]

A Management of acute neurovisceral attacks

B General measures

In the initial phase, especially in mild acute attacks (mild pain, no neuropathy, no hyponatraemia), patients may respond to conservative measures that they can initiate at home. However, if neurological features develop or the patient fails to respond to initial conservative measures within 12-18 hours, then admission for monitoring, treatment with parenteral analgesia, fluid replacement and possibly i.v. HA is indicated. As few clinicians have experience with managing an acute attack, advice should be sought from a porphyria specialist. Specialist support is provided in the UK through NAPS who provide 24-hour clinical advice.[23]

The following should be considered in patients experiencing an acute attack of porphyria:[3,19]

- Remove or treat precipitating factors and use non-porphyrinogenic medicines. A safe medicines list is provided by the UKPMIS.[21]
- Exclude other causes of abdominal pain including surgical, gynaecological, obstetric or post-operative complications.
- Conservative measures and increased oral carbohydrate intake may be sufficient to treat mild attacks.[9]
- Pain, nausea and vomiting are prominent features. Pain is usually severe and nearly always requires parenteral opioids, often in large doses.[13] Consider Patient Controlled Analgesia and seek advice from the local pain team as required. Antiemetics such as cyclizine, ondansetron and prochlorperazine are not porphyrinogenic.

- Heart rate, arrhythmias and blood pressure should be monitored. Hypertension and tachycardia should be managed with atenolol, propranolol or labetalol. Nifedipine is a safe alternative.
- Respiratory rate and oxygen saturations should be monitored. An arterial blood gas should be taken if there is concern about respiratory function.
- Observe muscle weakness as well as bladder and bowel dysfunction. Progressive neuropathy is a medical emergency. Affected patients should be transferred to a high dependency unit or intensive care, with access to specialist neurology and metabolic advice. Convulsions can be terminated with intravenous lorazepam, or diazepam. Safe anticonvulsants should be prescribed for ongoing use, e.g. levetiracetam.
- Fluid balance should be carefully monitored, especially if the patient is vomiting. Sodium chloride 0.9% or similar crystalloids may be needed to correct dehydration and electrolyte disturbance. Fluid replacement with glucose only solutions e.g. glucose 5% should be avoided as there is a risk of exacerbating hyponatraemia. In patients unable to tolerate oral calories, glucose 5% with sodium chloride 0.9% or similar crystalloids are suitable.
- Hyponatraemia occurs in up to 40% of cases and can be severe.[3] The exact mechanism of hyponatraemia during an acute attack is unclear. The syndrome of inappropriate antidiuresis and renal and/or gastrointestinal related sodium loss have all been described. A cause should be sought in each patient with specific attention to intravascular volume status. Hyponatraemia exclusively due to an acute attack of porphyria typically does not respond to fluid restriction alone and may require hypertonic saline.

- A random urine sample for urinary PBG should be collected and sent for laboratory analysis as described earlier.[16]

B Specific treatment: haem arginate (HA) therapy

Human haemin, available in the UK as haem arginate (Normosang®, Recordati Rare Diseases, Paris, France), is a specific therapy for severe acute neurovisceral attacks irrespective of the type of AHP.[26] Indications for the use of HA include progressive neuropathy, hyponatraemia, convulsions and persistent pain and vomiting unresponsive to conservative measures.[19] Despite reducing severity and duration of attacks in addition to progression of neuropathy HA will not reverse established nerve damage. The recommended dose of HA is 3mg kg^{-1} (maximum 250mg) once daily on four consecutive days. HA is supplied as a concentrated haem solution which is diluted in saline immediately prior to infusion and administered over 30-40 minutes (Table 3).[25] In the UK HA is obtained through the NAPS.[23]

The main side effect of acute administration of HA is local perivascular irritation and thrombophlebitis. This effect can be minimised by administration through a large bore cannula or central line in addition to flushing with 250ml sodium chloride 0.9% after the infusion. Frequent peripheral use may cause phlebitis of peripheral veins, whilst central lines can become obstructed with haem deposits after repeated administration.

A Conclusions

Despite being a rare condition, it is essential for anaesthetists to consider the practical implications of managing surgical patients with AHP. The variable and non-specific symptoms can make the diagnosis of an acute attack challenging. Advice on the management of these patients can be sought from the NAPS.[23] In the perioperative period, precipitating conditions should be avoided and drugs should be chosen from a safe list such as that provided by the UKPMIS.[21]

A Sources of further information

- British Porphyria Association. http://www.porphyria.org.uk/
- European Porphyria Network. https://porphyria.eu/
- Porphyria South Africa. http://www.porphyria.uct.ac.za/

Declaration of interests

The authors declare no external funding or conflicts of interests

References

1. Bissell DM, Anderson KE, Bonkovsky HL. Porphyria. *N Engl J Med* 2017; **377**: 862-72
2. Findley H, Philips A, Cole D, Nair A. Porphyrias: implications for anaesthesia, critical care, and pain medicine. *Continuing Education in Anaesthesia, Critical Care & Pain* 2012; **12(3**): 128-33
3. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. *Br J Haematol* 2017; **176**: 527–38
4. Elder G, Harper P, Badminton M, Sandberg S, Deybach JC. The incidence of inherited porphyrias in Europe. *J Inherit Metab Dis* 2013; **36**: 849-57
5. Chen B, Solis-Villa C, Hakenberg J, *et al*. Acute intermittent porphyria: predicted pathogenicity of HMBS variants indicates extremely low penetrance of the autosomal dominant disease. *Hum Mutat* 2016; **37**:1215-22
6. Meissner P, Adams P, Kirsch R. Allosteric inhibition of human lymphoblast and purified porphobilinogen deaminase by protoporphyrinogen and coproporphyrinogen. A possible mechanism for the acute attack of variegate porphyria. *J Clin Invest* 1993;**91**:1436-44
7. Meyer UA, Schuurmans MM, Lindberg RL. Acute porphyrias: pathogenesis of neurological manifestations. Semin Liver Dis 1998; **18(1)**: 43-52
8. Hift RJ, Thunell S, Brun A. Drugs in porphyria: from observation to a modern algorithm-based system for the prediction of porphyrogenicity. *Pharmacol Ther* 2011; **132:** 158–69

9. Handschin C, Lin J, Rhee J et al. Nutritional regulation of hepatic heme biosynthesis and porphyria through PGC-1alpha. *Cell* 2005; **122(4)**: 505-15
10. Anderson KE, Bradlow HL, Sassa S, Kappas A. Studies in porphyria. VIII. Relationship of the 5 alpha-reductive metabolism of steroid hormones to clinical expression of the genetic defect in acute intermittent porphyria. *Am J Med* 1979; **66**: 644–50
11. Marsden JT, Rees DC. A retrospective analysis of outcome of pregnancy in patients with acute porphyria. *J Inherit Metab Dis* 2010; **33**: 591-6.
12. Doss MO, Kühnel A, Gross U. Alcohol and porphyrin metabolism. *Alcohol Alcohol* 2000; **35**: 109–25
13. Hift RJ, Meissner PN. An analysis of 112 acute porphyria attacks in Cape Town, South Africa. *Medicine* 2005; **84**: 48-60
14. Gouya L, Ventura P, Balwani M, *et al*. EXPLORE: A Prospective, Multinational, Natural History Study of Patients with Acute Hepatic Porphyria with Recurrent Attacks. *Hepatology* 2020; **71(5)**: 1546-58
15. Deacon AC, Elder GH. ACP best practice no 165: front line tests for the investigation of suspected porphyria. J Clin Pathol 2001; **54**: 500–7
16. Woolf J, Marsden JT, Degg T, *et al.* Best practice guidelines on first-line laboratory testing for porphyria. *Ann Clin Biochem* 2017; **54**: 188-98
17. Marsden JT, Rees DC. Urinary excretion of porphyrins, porphobilinogen and δ-aminolaevulinic acid following an attack of acute intermittent porphyria. *J Clin Pathol* 2014; **67**: 60-5
18. Whatley SD, Mason NG, Woolf JR et al. Diagnostic strategies for autosomal dominant acute porphyrias: retrospective analysis of 467 unrelated patients

referred for mutational analysis of the HMBS, CPOX or PPOX gene. Clin Chem 2009; **55**: 1406-14

19. Stein P, Badminton M, Barth J, Rees D, Stewart MF. Best practice guidelines on clinical management of acute attacks of porphyria and their complications. *Ann Clin Biochem* 2013; **50**: 217–23
20. James MF, Hift RJ. Porphyrias. *Br J Anaesth* 2000; **85**: 143-53
21. UK Porphyria Medicines Information Service. Provided by the Welsh Medicines Information Centre. 2019 Porphyria Safe List. Available from https://www.wmic.wales.nhs.uk/specialist-services/drugs-in-porphyria/ (accessed 05 March 2020)
22. Green, SM, Leroy, PL, Roback, MG et al. An international multidisciplinary consensus statement on fasting before procedural sedation in adults and children. Anaesthesia 2020; **75**: 374-85
23. National Acute Porphyria Service contact details: Cardiff porphyria service. Available from www.cardiff-porphyria.org. King's College Hospital porphyria service https://www.kch.nhs.uk/service/a-z/porphyria (Accessed 31st July 2020).
24. Saberi K, Salehi M, Rahmanian M, Bakhshandeh AR, Mahlabani M. Anesthetic implication of tricuspid valve replacement in a patient with acute intermittent porphyria. *Ann Card Anaesth* 2016; **19(2)**: 367–71
25. Summary of Product Characteristics - Normosang® (Haem arginate) Recordati Rare Diseases. Available from https://www.medicines.org.uk/emc/product/6235 (Accessed 21 February 2020)

26. American Porphyria Foundation. Drug Database, available from https://www.porphyriafoundation.org/drugdatabase/ (Accessed 05/08/2020)

Figure Legend

Figure 1. Haem biosynthesis pathway.

AIP, acute intermittent porphyria; ALA, aminolevulinic acid; ALAD, ALA dehydratase; CEP, congenital erythropoietic porphyria; HCP, hereditary coproporphyria; HEP, hepatoerythropoietic porphyria; HMB, hydroxymethylbilane; PBG, porphobilinogen; PCT, porphyria cutanea tarda; VP, variegate porphyria.

Porphyrias in bold present with acute neurovisceral attacks. Two acute porphyrias, VP and HCP, can present with acute attacks and/or photosensitivity. HMB is a linear tetrapyyrole, made from 4 porphobilinogen molecules, which forms the first of the cyclic ring structures, uroporphyrinogen III.

Gain of function mutations in the ALAS2 gene result in increased synthesis of free protoporphyrin IX in erythroid cells causing acute photosensitivity and not acute attacks.

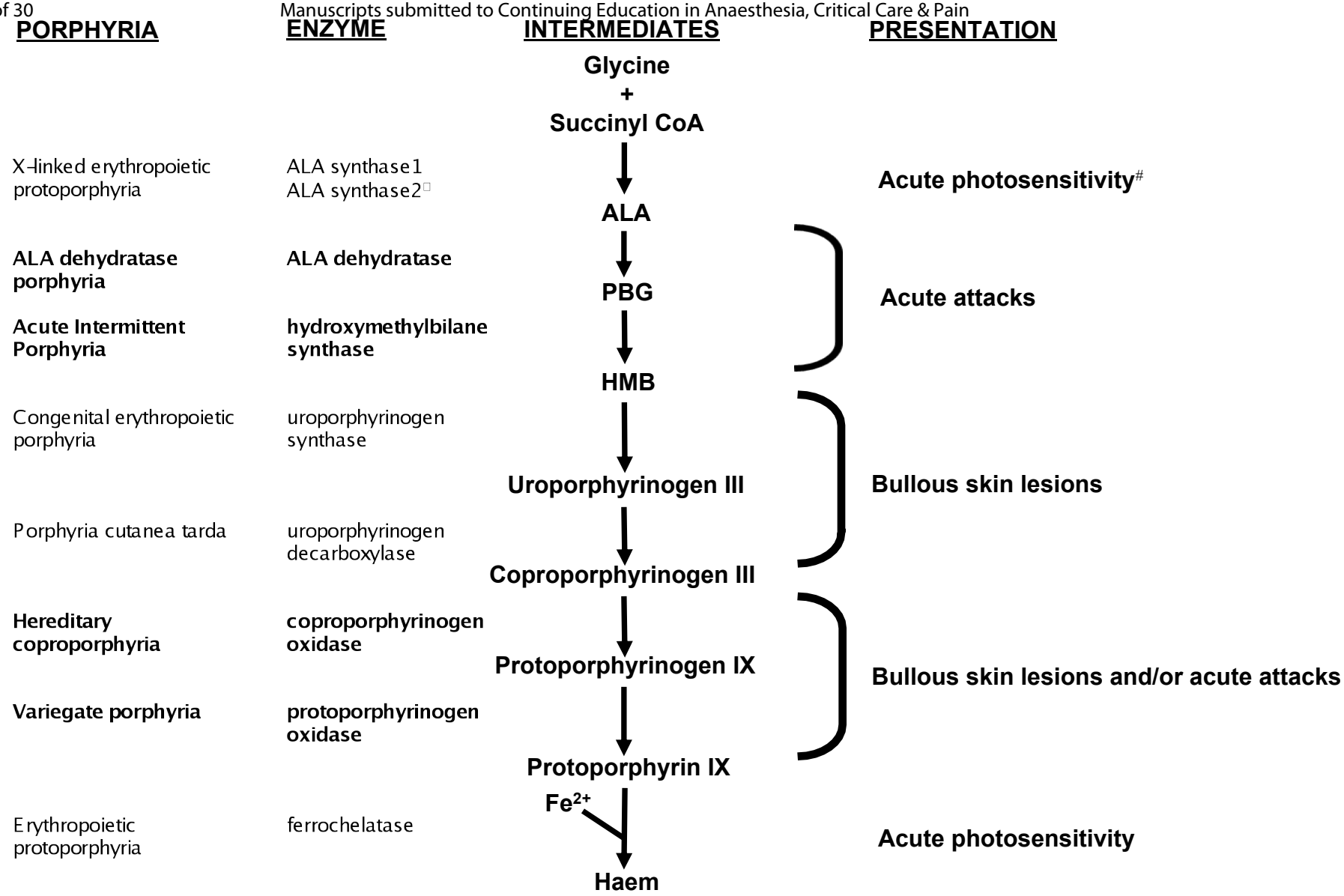
PORPHYRIA
ENZYME
INTERMEDIATES
PRESENTATION
Glycine
+
Succinyl CoA
X-linked erythropoietic protoporphyria
ALA synthase1
ALA synthase2
ALA
Acute photosensitivity#
ALA dehydratase porphyria
ALA dehydratase
PBG
Acute Intermittent Porphyria
hydroxymethylbilane synthase
HMB
Acute attacks
Congenital erythropoietic porphyria
uroporphyrinogen synthase
Uroporphyrinogen III
Porphyria cutanea tarda
uroporphyrinogen decarboxylase
Coproporphyrinogen III
Bullous skin lesions
Hereditary coproporphyria
coproporphyrinogen oxidase
Protoporphyrinogen IX
Variegate porphyria
protoporphyrinogen oxidase
Protoporphyrin IX
Bullous skin lesions and/or acute attacks
Fe2+
Erythropoietic protoporphyria
ferrochelatase
Haem
Acute photosensitivity

Table 1. Key biochemistry abnormalities of porphyin distinguishing the autosomal dominant acute porphyrias.[18]

Porphyria Type	Urine ALA and PBG*	Faecal Porphyrins	Plasma porphyrin fluorescence emission peak wavelength (nm)
Acute intermittent porphyria	↑↑↑↑	Not Increased	↑ 615-620 or none
Hereditary coproporphyria	↑↑	↑↑↑ Copro III	↑ 615-620 or none
Variegate porphyria	↑↑	↑↑↑ Proto ↑↑ Copro III	↑↑↑ 624-627

ALA, aminolaevulinic acid; CoproIII, Coproporphyrin III isomer; PBG, porphobilinogen; Proto, protoporphyrin; Uro, uroporphyrin.

* PBG and ALA usually return to normal between acute attacks in hereditary coproporphyria and variegate porphyria.

Table 2. Medicines used regularly during the perioperative period. The evidence underpinning the classification for each drug can be reviewed in the Drug Database for Acute Porphyria (https://www.drugs-porphyria.org) by selecting the Info Tab to access a drug monograph.

	Safe	Unsafe	No Data Available
Local Anaesthesia			
Dental	Articaine ± adrenaline (epinephrine) Lidocaine ± adrenaline Mepivacaine ± adrenaline Prilocaine ± felypressin		
Regional Anaesthesia	Bupivacaine Prilocaine Levobupivacaine Ropivacaine		Procaine
Topical Anaesthesia	Tetracaine eye drops (0.5-1%) Tetracaine gel (4%) Lidocaine gel 2% Lidocaine spray Oxybuprocaine eye drops (0.4.%)		
General Anaesthesia			
Induction	Propofol	Esketamine Etomidate Ketamine Thiopentone	
Inhalational	Desflurane Enflurane Isoflurane Nitrous Oxide Sevoflurane	Halothane	
Muscle Relaxants and Reversal agents	Atracurium Cisatracurium Mivacurium Neostigmine Pancuronium Rocuronium Sugammadex Suxamethonium Vecuronium		

Medicines used during perioperative care			
Analgesia	Clonidine Diclofenac Gabapentin Ibuprofen Ketoprofen Ketorolac Naproxen Opioids (alfentanil, diamorphine, fentanyl, morphine, oxycodone, pethidine, remifentanil, tramadol) Paracetamol Parecoxib Pregabalin	Dexmedetomidine	Flurbiprofen Papaveretum Pentazocine
Antibiotics/ antifungals and antivirals	Aciclovir Anidulafungin Aminoglycosides Amphotericin Caspofungin Cefuroxime Ceftriaxone Co-amoxiclav Levofloxacin Linezolid Meropenem Metronidazole Penicillins* Piperacillin with tazobactam Quinolones Vancomycin	Clarithromycin Clindamycin Erythromycin Fluconazole Itraconazole Rifampicin Sulfamethoxazole Trimethoprim	
Antiemetics	Cyclizine Domperidone Granisetron Metoclopramide Ondansetron Prochlorperazine		
Cardiovascular medicines	ACE inhibitors Adenosine Adrenaline/Epinephrine Amlodipine Atenolol Atropine	Amiodarone Diltiazem Hydralazine Indapamide Methyldopa Metolazone	Metaraminol Vasopressin Enoximone

	Bumetanide Digoxin Dopamine Ephedrine Eplerenone Esmolol Furosemide Glyceryl trinitrate Glycopyrronium bromide Labetalol Metoprolol Milrinone Nifedipine Nimodipine Noradrenaline (norepinephrine) Phenylephrine	Spironolactone Verapamil	
Central nervous system	Diazepam Flumazenil Haloperidol Levetiracetam Lorazepam Midazolam Naloxone Temazepam Zopiclone	Flunitrazepam Nitrazepam Sodium valproate Phenytoin Phenobarbital	
Fibrinolytics, anticoagulants	Alteplase Apixaban Clopidogrel Heparin Low Molecular Weight Heparins Rivaroxaban Streptokinase Tenecteplase Ticagrelor Warfarin		
Obstetrics and gynaecology	Atosiban Carboprost Misoprostol Oxytocin	Ergometrine[§] Mifepristone	
Respiratory	Aminophylline Beclomethasone Budesonide		

	Ipratropium Salbutamol Salmeterol Terbutaline Tiotropium		
Miscellaneous	Acetazolamide Acetylcysteine Chlorphenamine Contrast media (gadolinium-based, gastrografin, iodine-based) Dexamethasone Glucagon Hydrocortisone Hyoscine Insulins Magnesium Protamine† Proton pump inhibitors Sodium Bicarbonate Tranexamic acid		Dantrolene Phentolamine

*There are conflicting reports on the safety of flucloxacillin. Use only if there is no safe alternative.

† Protamine is considered safe by the American Porphyria Foundation[26]

§ Use if required in an obstetric emergency.

In an emergency, any drug considered essential to patient survival can be given. Omission of a medicine does not necessarily mean it is unsafe, further information can be obtained from the UKPMIS who can also be contacted by telephone. Information on medicine safety was collated from the UKPMIS safe drugs list,[21] the Drug Database for Acute Porphyria (https://www.drugs-porphyria.org) and the American Porphyria Foundation Safe Drug list (https://www.porphyriafoundation.org/drugdatabase/) accessed 5th August 2020.

Table 3: Practical information on giving haem arginate.[25]

Giving haem arginate	
Establish venous access	• Large i.v. cannula OR: • Peripherally inserted central catheter line (PICC) OR: • Central line
Equipment	Giving set with 15-20 micron inline filter
Preparation	Dilute immediately before giving • 3 mg kg-1 (maximum 250 mg) in 100 ml saline 0.9% once daily for four consecutive days • Do not exceed 5 mg kg-1 daily
Infusion	• Infuse over 30 to 40 minutes • Monitor infusion site continuously for extravasation
Aftercare	Flush using 250 ml sodium chloride 0.9% solution: • Three to four 10 ml boluses initially, then: • Remaining volume under gravity
Other	• Alternate arms daily if peripheral infusion • Stop infusion immediately in case of extravasation