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PORPHYRIA

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CONTENTS

PORPHYRIA

INTRODUCTION

The porphyrias are a group of mostly inherited metabolic disorders of haem biosynthesis. The complex pathway involved in haem biosynthesis is governed by a sequence o fenzymes. A defect in any of these enzymes results in accumulation of the porphyrin precursors and is responsible for the clinical signs and symptoms seen in an Acute Porphyric Crisis.

Porphyria dates back to the time of King George III of England who, based on the notes of his attending physicians, is suspected to have suffered from Variegate Porphyria. He suffered frequent bouts of symptoms similar to those present in an acute porphyric attack: abdominal pain, dark red urine, weakness of his limbs and psychosis. He would recover spontaneously. However, it was these frequent episodes that was thought to have contributed to Britain's losses to the American Revolutionaries in the 18th century

The identification of patients with Porphyria is difficult as it is estimated that only 20% of patients with the enzyme defect are symptomatic with the majority of individuals with the disease remaining asymptomatic throughout their lives. Also, affected individuals may show no biochemical abnormalities during the asymptomatic phase.

Although this condition is rare, with the overall frequency of porphyria in Europe being approximately 1 in 20 000 and 1 in 10 000 in Northern Sweden, Variegate Porphyria is most common in South Africa with a reported prevalence of 1 in 250-500[(1)] in the Afrikaaner population.

Anaesthesia has been implicated in triggering several severe acute prophyric crises. This potentially fatal complication can be avoided if we have a greater awareness of the condition and take the proper precautionary measures.

PATHOPHYSIOLOGY

The porphyrins, which are cyclic structures formed by the linkage of 4 pyrrole rings, play an important role in biology. The biologically significant porphyrin is HAEM which is found in haemoglobin, myoglobin and the cytochromes.

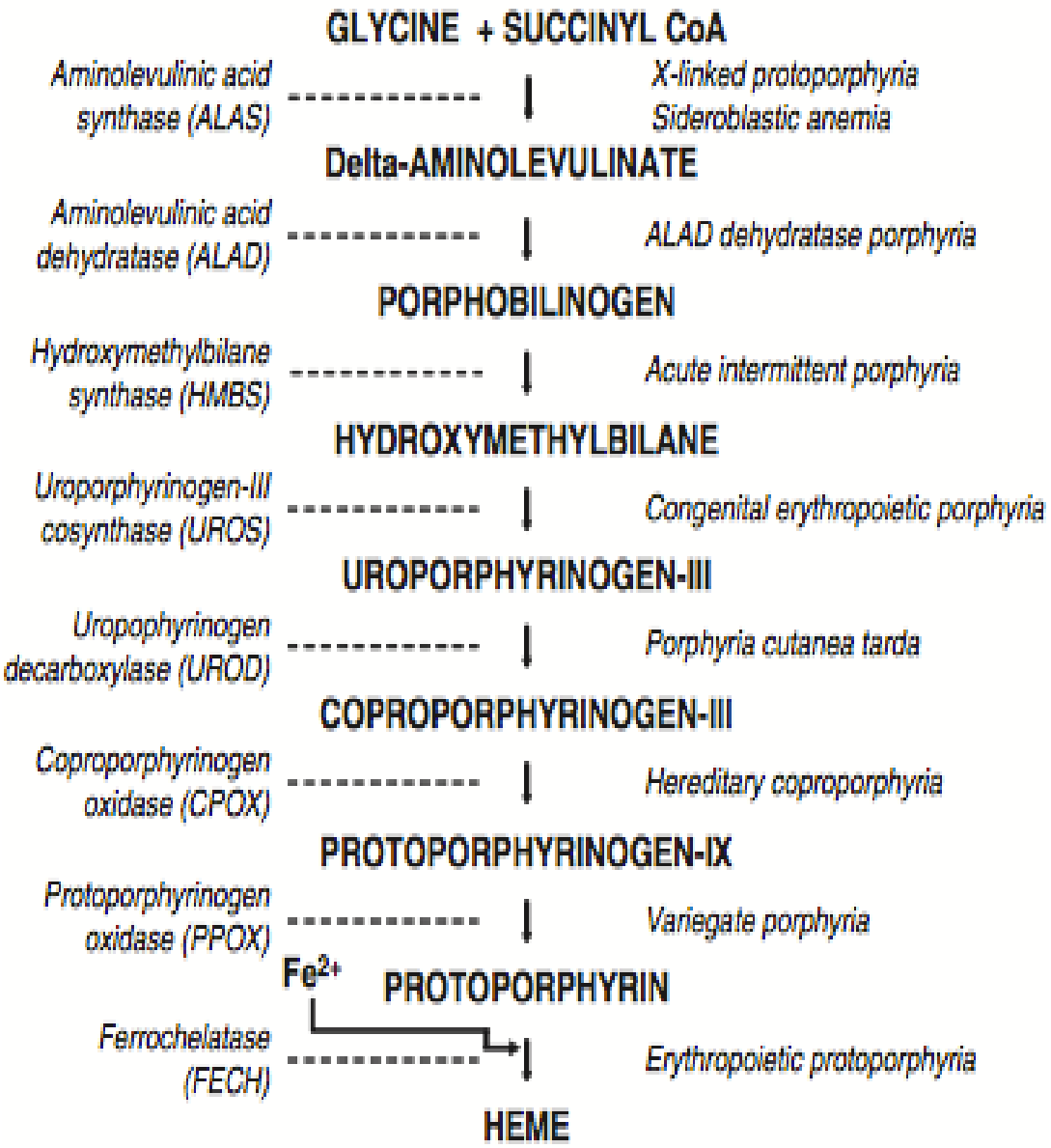


Image 1: Haem biosynthetic pathway (1)

The first step of the biosynthetic pathway involves the condensation and decarboxylation of succinyl-coA and glycine to form aminolaevulinic acid (ALA). This reaction is catalysed by ALA synthase. This occurs in the mitochondria after which aminolaevulinic acid moves into the cytoplasm where the subsequent enzymatic reactions occur. 2 ALA molecules are condensed, under the influence of ALA dehydratase, which forms porphobilinogen (PBG).

Four molecules of PBG then condense to form hydroxymethylbilane which is converted to uroporphryinogen. This is catalysed by PBD deaminase and Uroporphyrinogen cosynthase, respectively. Uroporphyrinogen is then converted to Coproporphyrinogen which re-enters the mitochondria and is chelated with ferrous iron to form haem.

The first step is the most important rate-limiting step and the control of haem production is mainly dependant on ALA synthase. Abnormalities in the enzymatic activity of ALA synthase or deficiencies of this enzyme results in sideroblastic anaemia which is a heterogenous group of disorders that results in the production of abnormal erythrocytes (ringed sideroblasts). This condition is not linked to porphyria and may be inherited (X-linked or autosomal recessive) or acquired. The clinical presentation of sideroblastic anaemia also differs from porphyria.

The concentration of haem within the cytosol of the cell forms a negative feedback loop which controls the formation and induction of ALA synthase. Increased haem requirements results in induction of ALA synthase. This poses a problem in the presence of partial block in the synthetic pathway due to deficiency of an enzyme as an increase in production and activity of ALA synthase will result in an increase in the pathway intermediates before the deficient enzyme.

Accumulation of porphyrinogens (uroporphyrinogen and coproporhyrinogen) and porphyrins are responsible for the clinical manifestations of an Acute Porphyric Attack which result from central, peripheral and autonomic neuropathy. The exact mechanism for neurological damage in an acute porphyria crisis is not yet completely understood but it is suggested that ALA or a metabolite of ALA may be a direct neurotoxin. Another hypothesis is that haem deficiency within the nerve cell results in a decrease in haem-containing enzymes within the cell which are responsible for production of neurotransmitters such as serotonin.

CLASSIFICATION OF PORPHYRIAS

The porphyrias may be classified based on 3 characteristics:

- The site of the enzyme defect: Hepatic or Erythropoietic Porphyrias

- The specific enzyme defect:
  ALA dehydratase: Plumboporphyria
  PBG deaminase: Acute Intermittent Porphyria
  Uroporphrinogen cosynthase: Congenital Erythropoietic Porphyria
  Uroporphyrinogen decarboxylase: Porphyria Cutanea Tarda
  Coproporphyrinogen Oxidase: Hereditary Coproporphyria
  Protoporphyrinogen Oxidase: Variegate Porphyria

- Whether or not they cause acute symptoms
  Acute and Non-acute Porphyrias
  All hepatic porphyrias cause acute symptoms except Porphyria Cutanea Tarda.
  Therefore, the porphyrins that cause acute symptoms include: ***Acute Intermittent Porphyria, Porphyria Variegate, Hereditary Corproporphyria*** and ***Plumboporphyria.***

Erythropoeitic porphyrias cause extreme skin sensitivity but lack neurologic involvement and are not associated with drug precipitated acute porphyric crisis. The Acute Porphyrias are the most clinically significant in Anaesthetic practice. Drugs used during Anaesthesia may trigger an acute attack. Except for Plumboporphyris, the Acute Porphyrias are inherited as non-sex-linked, autosomal dominant conditions with variable expression.

Diagnosis of the Acute Porphyrias

Porphyria should not be diagnosed based on clinical signs and symptoms alone. In South Africa, the laboratory techniques and diagnostic approach is based on the fact that South Africa has a high incidence of one type of porphyria (variegate porphyria) resulting from a single founder mutation (R59W).

The most appropriate test for detection of Porphyria in a patient will be dependant on the type of porphyria suspected based on the family history. DNA analysis is most appropriate if the family mutation is known. If the family mutation is not known or there is uncertainty regarding the accuracy of the family history of porphyria then blood and urine samples should be sent to screen for all types of porphyria.

This is done by erythrocyte and plasma fluorescence scanning and urine chromatography. Erythrocyte flourescence is useful in detecting erythropoietic protoporphyria and congenital erythropoietic porphyria. Plasma flourescence is able to detect variegate porphyria, acute intermittent porphyria and porphyria cutanea tarda. Urinary chromatography is used to detect urinary ALA, PBG and porphyrin concentration for the diagnosis of an acute attack. It is also helpful in providing information about disease activity irrespective of which type of porphyria is present as there is a relationship between the degree of elevation of urinary ALA, PBG and porphyrin and the likelihood that the acute symptoms are due to porphyria. DNA analysis is also important in order to screen other family members for the same gene mutation. Stool porphyrin scanning is longer done routinely in South Africa as the plasma porphyrin scan has been noted to have greater simplicity, specificity and sensitivity. Stool scanning is reserved for specific indications (i.e the diagnosis of hereditary coproporphyria).

Disorder	Phase	Urinary ALA and PBG	Urinary porphyrins	Faecal porphyrins
AIP	quiescent	increased	mild increase	normal
	acute	very high	very high	as above
HCP	quiescent	normal	coproporphyrin III often increased	increased coproporphyrin III
	acute	high	increased	as above
VP	quiescent	normal	normal	increased pentacarboxylic porphyrin III, coproporphyrin III and protoporphyrin IX
	acute	high	high	as above

Table 1: Summary of biochemical findings in the acute porphyrias [2]

In South Africa, all specimens are sent to the MRC/UCT Liver Research Centre in the Western Cape.

ABOUT VARIEGATE PORPHYRIA

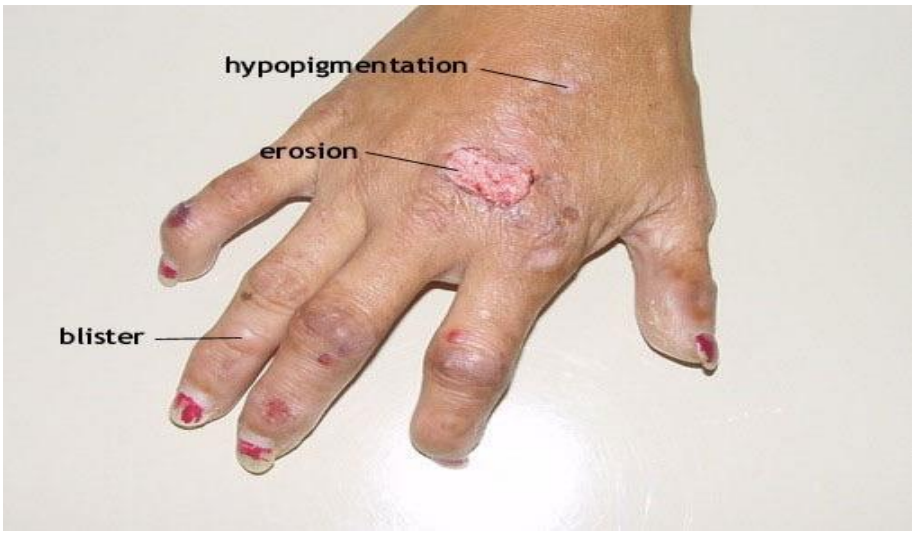
Variegate Porphyria is the commonest inherited disorder encountered in South Africa.

The gene for the South African form of variegate porphyria was introduced into South Africa by two Dutch settlers (Gerrit Jansz and Adriaantje Ariens) in 1688. This gene spread widely throughout the South African population and is common amongst South Africans of Dutch ancestry. Males and females are equally affected.

The enzyme defect: Protoporphyrinogen oxidase. The R59W mutation is found in 95% of the South African population and can be tested for. The enzyme defect results in the accumulation of protoporphyrin and coproporphyrin.

Clinical Manifestations:

- Patients experience skin manifestations from deposition of porphyrins in the skin. Lesions develop in sun-exposed areas and appear as fluid-filled blisters and small erosions. Chronic appearances of the skin lesions consist of small areas of hypo or hyper pigmentation.
- Patients are also at risk for developing an acute porphyric crisis.



- Only 40% of patients may be symptomatic, the rest remain quiescent

Image 2: Skin lesions in variegate porphyria[2]

Diagnosis

- Plasma fluoroscanning: Porphyrins are able to absorb UV light at different wavelengths. A plasma flourescence peak at 625nm indicates a positive test.
- Demonstration of elevated protoporphyrin and coproporphyrin in stool
- DNA analysis with demonstration of R59W mutation

ACUTE PORPHYRIC CRISIS

The enzyme deficiencies in Acute Porphyria are only partial. In most patients, the level of enzyme reduction is around 50%. These enzyme deficiencies predispose affected individuals to developing an acute attack during events that increase haem concentrations. Acute attacks can range from mild disturbances to severe and life-threatening.

Precipitating Factors:

1. Prolonged fasting
2. Alcohol
3. Drugs: especially those that induce cytochrome P450
4. Smoking
5. Stress (psychological and physical)
6. Intercurrent illness
7. Physiological hormone variation
8. Infection

Signs and Symptoms

Acute symptoms involve central, peripheral and autonomic nervous systems.

Central Symptoms: Agitation, psychosis

Peripheral Symptoms: Progressive peripheral neuropathy, muscle weakness which may progress to quadriparesis and respiratory failure requiring mechanical ventilation.

Autonomic Symptoms: Severe, diffuse abdominal pain. No signs of peritonism. This is thought to be due to autonomic neuropathy. Nausea, vomiting and constipation or diarrhoea. Hypertension and tachycardia, postural hypotension, urinary incontinence or retention.

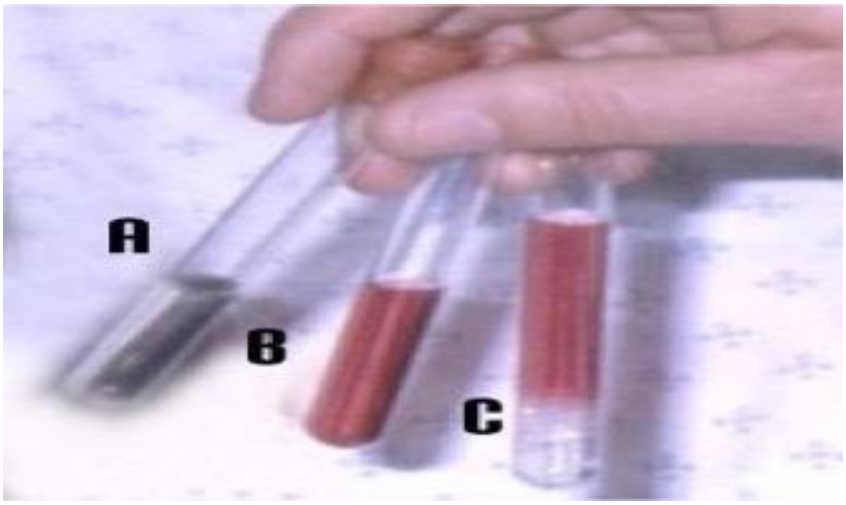
Symptoms and Signs	Frequencies of Symptoms and Signs (%)	Comment
Gastrointestinal		
Abdominal pain	85–95	Usually unremitting (for hours or longer) and poorly localized but can be cramping.
Vomiting	43–88	Neurologic in origin and rarely accompanied by peritoneal signs, fever, or leukocytosis.
Constipation	48–84	Nausea and vomiting often accompany abdominal pain. May be accompanied by bladder paresis.
Diarrhea	5–12	
Neurologic		
Pain in extremities, back	50–70	Pain may begin in the chest or back and move to the abdomen. Extremity pain chest, neck, or head indicates involvement of sensory nerves; objective sensory loss reported in 10–40% of cases.
Paresis	42–68	May occur early or late during a severe attack. Muscle weakness usually begins proximally rather than distally and more often in the upper than lower extremities.
Respiratory paralysis	9–20	Preceded by progressive peripheral motor neuropathy and paresis.
Mental symptoms	40–58	May range from minor behavioral changes to agitation, confusion, hallucinations, and depression.
Convulsions	10–20	A central neurologic manifestation of porphyria or due to hyponatremia, which often results from syndrome of inappropriate antidiuretic hormone secretion or sodium depletion.
Cardiovascular		
Tachycardia	64–85	
Systemic arterial hypertension	36–55	May require treatment during acute attacks, and sometimes becomes chronic.

Table 2: Common signs and symptom and the frequency with which they occur[2]

Other complications of an acute attack:
Biochemical Abnormalities: hyponatremia, hypomagnesaemia, hypochloraemia, hypokalaemia
Seizures: Tonic-clonic. This may be associated with hyponatremia and enkephalopathy
Renal Failure.
Photosensitivity: Bullous skin rash (in VP and HCP)

Diagnosis of an Acute Attack
An acute porphyric crisis is confirmed by:
- biochemical assays which detect raised concentrations of the haem biosynthetic pathway intermediates in urine, faeces and erythrocytes.
- the Watson-Schwartz reaction (screening test for acute porhyric crisis)
Urine is placed in a test tube. An equal volume of Ehrlich's aldehyde is added. A weakly positive reaction is denoted by a rose-pink colour and a strongly positive reaction by a red colour. Chloroform is added to determine whether the pink/red colour is due to the presence of PBG or urobilinogen. The tube is mixed and allowed to settle. If the red colour remains in the top, aqueous phase, this confirms the presence of PBG. If the red colour remains at the bottom, the urine contains urobilinogen.

Image 2: Watson-Swartz Reaction[1]



- Another crude test for the presence of PBG in urine can be done by placing a sample of urine in light. Porphyrinogens are colourless but convert to porphyrins in light and makes the urine turn a port wine colour.

Differential diagnosis of acute porphyric crisis[(7)]:
Surgical causes for acute abdomen: Appendicitis, pancreatitis, cholecytitis, etc.

Addisonian crisis	Hypertensive crisis
Pheochromocytoma	Tachyarrhythmia
Acute hypoparathyroidism	
Guillain-Barre Syndrome	Acute haemolytic crisis
Delirium	
Epilepsy	Acute gastroenteritis

Management
Management of an Acute Porphyric Crisis includes specific and supportive measures.

Supportive Measures:
1. Immediate cessation of any medication that is not known to be safe in porphyria
2. Pain management: patients require frequent, high doses of opiate analgesia as pain is severe and recurs after a short interval. Opiate dependence in acute porphyria is rare as the need for high, frequent doses of opiates is genuinely in response to excruciating pain.

Recommended analgesic agents:
- Pethidine: patients may require 50-100mg hourly
- Morphine

Drugs to avoid:
- Antispasmodics (e.g. Hyoscine butylbromide)
- These may precipitate an acute attack.

3. Vomiting and Nausea: Recommended antiemetics:
- Metoclopramide, prochlorperazine

4. Hypertension and Tachycardia: hypertension is usually mild and subsides without specific treatment. In cases of severe hypertension Beta-adrenergic and Alpha-adrenergic blockers can be used. Beta-blockers are, in themselves, anti-porphyrinogenic and are therefore beneficial. Magnesium sulphate may also be added in the rare event of severe hypertension not responding to Beta and Alpha-adrenergic blockers.

5. Fluid therapy and Carbohydrate intake[15].
Patients with acute porphyria are often dehydrated due to vomiting and poor oral intake. Electrolyte imbalance is also common. These include: hyponatremia, hypomagnesemia and hypokalaemia. Decreased caloric intake may precipitate or worsen an acute porphyric crisis. Therefore, an adequate fluid and carbohydrate intake is important.

Recommended Fluid Therapy:
- 5% Dextrose Saline (2 litres will provide 100g of glucose a day)
- As soon as patients are able to tolerate oral intake the should be transferred to a diet in which carbohydrates provide 55-60% of the energy needed to maintain their normal weight.

6. Seizures: Seizures may be due to the neuropathy caused by the disease itself or secondary to the electrolyte abnormalities that may occur.

Recommended drug therapy:
- Clonazepam and Diazepam

7. Psychosis: chlorpromazine is suitable in the treatment of psychosis.

8. Correct electrolyte imbalances.

9. Investigate for and treat infections.

Specific Treatment:
40% of Acute Attacks, especially those occurring in patients with Variegate Porphyria, will resolve with supportive management alone. Patients with severe attacks, recurrent episodes or patients that show no improvement after 24 hours require specific treatment.

1. Haem Arginate vs Haematin
Typically, haem therapy has been given in the form of hematite which consists of haem dissolved in alkali. This solution, however, is unstable and rapidly decomposes. The resultant degradation products are said to be responsible for some of the adverse reactions seen with the use of Haematin. Haem complexed with the amino acid arginine forms the stable compound: Haem araginate. Both Haematin and Haem arginate works by replenishing haem stores and thereby inhibiting ALA synthetase by the negative feedback mechanism. Further build up of porphyrins are therefore prevented.

Complications:
- Phlebitis at the site of injection has been reported with the use of Haem arginate: this can be reduced by diluting the drug in human serum or human serum albumin which acts as a protein buffer.
- Phlebitis has also been noted with the use of Haematin as well as dose-related, reversible renal shutdown and thrombocytopenia and coagulopathy.

Disadvantages:
- Haem arginate is extremely expensive (currently costs around R20000 for 4 ampoules)
However, the dramatic clinical improvement and shortened hospital stay with a course of haem arginate therapy as compared to long term hospitalisation and rehabilitation without haem arginate, makes haem arginate highly cost effective.

Ways in which to minimise cost include:
- Reserving treatment for patients with severe acute porphyric attack, recurrent episodes or no improvement after 24 hours, with conservative management. It is reasonable to closely observe patients for 24 hours and treat with supportive measures before deciding to commence treatment with Haem arginate.
- Using a standard dose of 5ml per dose (instead of the 3mg/kg/day advised on the package insert). Each vial contains 10ml. The standard dose has been shown to be effective.
- It is vitally important that haem arginate is given before neuropathy develops as it does not reverse already established neuropathy.
- Haem arginate is not FDA approved.
- Haematin is extremely unstable.

Obtaining Haem Arginate (Normosang™) in South Africa:
Supplier: Equity Pharma
Telephone number: 012 345 1747
Fax: 012 345 1412

2. Cimetidine

Cimetidine decreases haem oxidase activity thereby decreasing haem consumption and providing some negative feedback on ALA synthetase. It was thought that cimetidine could be used as a prophylactic drug to prevent acute attacks, however, human studies have not been confirmatory.

3. Somatostatin together with plasmapheresis has also been used and was found to decrease the rate of formation of ALA synthase, reduce pain and result in remission of symptoms.

PERIOPERATIVE CONSIDERATIONS

Anaesthesia has been implicated in triggering many acute porphyric crises. Delivering a safe anaesthetic to patients with symptomatic or asymptomatic Acute Porphyria is dependant on the detection of susceptible individuals and identification of porphyrogenic agents. This can be challenging and even more so when a patient presents with an acute porphyric attack and a concurrent or precipitating illness that requires surgical intervention (e.g. infection).

Regulating the drugs that patients with porphyria are exposed to is essential in the management of such patients. At the same time, this is quite challenging as patients may respond differently to the same drugs at different times and in different ways (i.e precipitation of an acute attack, clinically insignificant increase in porphyrin excretion, no clinical or biochemical response). This poorly understood inter-drug and inter-individual variation makes it difficult to predict which drugs are porphyrinogenic and which are safe.

Initially, identification of porphyrinogenic drugs was dependant on clinical experience. This proved to be imprecise and unreliable. Certain properties of drugs have been suggested in determining the probability that a drug is porphyrogenic.

Table 2: Drug porphyrogenicity based on drug properties[3]

Drug properties which should be considered in the determination of possible porphyrogenicity (Thunell et al., 2007). Factors 1 and 2 are prerequisites for porphyrogenicity; their absence suggests that it is highly unlikely that a drug is significantly porphyrogenic. Factors 3–5 require individual assessment and quantitation, and bear on the probability that a drug is porphyrogenic or not (expressed in drug safety lists as *possibly* or *probably* porphyrogenic, or *possibly* or *probably* non-porphyrogenic).

1	The drug is administered via a route and insufficient dosage to access the hepatic circulation in significant concentrations.	This usually requires oral or intravenous administration, or intramuscular administration with significant systemic absorption. For oral administration, they should be no significant first-pass gastric extraction. Administration via other routes, including topical or inhalation, is unlikely to be dangerous unless associated with unusual circumstances resulting in significant systemic absorption.
2	The drug is lipophilic and non-ionic.	This favours access to the hepatocyte and the microsomal system; charged molecules tend to be removed rapidly from the systemic circulation via renal excretion.
4	The drug has the potential to access the hepatocyte nucleus and bind to the nuclear receptors PXR or CAR.	Though this is not essential in the case of mechanism-based CYP inhibitors.
5	The drug is a CYP inducer with affinity for CYP3A4, or is a multifunction inducer, or is a mechanism-based inhibitor of CYP.	All three properties result in an increased heme requirement.
6	Exposure to the drug leads to the increased transcription of apoCYPs and ALAS1.	This is the final common pathway and appears to be common to all porphyrinogenic drugs.

Drugs can now be tested for in cell culture and animal models (by administering known porphyrinogenic agents to or genetically modifying rodents in order to mimic porphyria). While these models also have their limitations (overestimation of porphyrinogenicity of drugs), they have been useful in developing Drug Safety Lists.

In South Africa drugs are categorised as:

- USE: Drugs that are likely to be safe and may be used freely.
- USE WITH CAUTION (UWC): Safety is not established beyond doubt, evidence suggests that the drug is unlikely to prove unsafe. use the drug if no safer alternative is available.
- USE WITH EXTREME CAUTION ONLY (UWECO): Too little evidence exists to suggest this drug is safe or grounds to suspect that the drug may prove unsafe in practice. Only use this drug if the expected benefits outweigh the risks.
- AVOID: These drugs have precipitated acute attacks in patients or there are other grounds for believing that the risk of acute attack is high.
- NO DATA: There is too little evidence to draw a conclusion.

The total amount of a drug that a patient is exposed to and the length of time for which a patient is exposed to a drug may be related to the porphyrinogenicity of the drug.
The availability of newer, short-acting drugs has contributed to the safety of modern anaesthetic techniques.

Preoperative Evaluation:
A detailed family history and past medical history should be taken to try and elucidate the presence of porphyria and patients with any suggestion of porphyria in their history should be investigated further. If the urgency of the surgery precludes further investigation, patients should be treated as a porphyric patient until they are able to be investigated further. Many patients, however, will have no clinical evidence of the disease other than possible skin lesions. Acute porphyria should be suspected in any patient presenting with the symptoms prevalent in acute porphyria especially if clinical evaluation is not suggestive of any other possible causes.

A thorough physical examination must be done, looking especially for neurological abnormalities, cardiovascular instability and respiratory muscle function. Patients must be adequately hydrated with intravenous fluids (5% Dextrose saline)and long periods of starvation avoided. Investigations to detect electrolyte disturbances must be done. Good anxiolysis is advantageous as stress can precipitate acute porphyria.
Premedication: benzodiazepines are categorized as “Use With Caution”.

Intraoperative Management:
Regional Anaesthesia:
Acute Porphyria is not an absolute contraindication to regional anaesthesia. However, regional anaesthesia is best avoided in acute porphyric crises due to changes in mental status resulting in poor patient cooperation, haemodynamic instability and progressive neuropathy which may should differentiation between onset of anaesthesia and polyneuropathy associated with the disease. Prilocaine, bupivacaine, tetracaine and procaine have been used with safety.

General Anaesthesia:

Induction Agents:

All barbiturates are considered unsafe. Even though there have been reported cases in which Thiopental has been used safely in patients with aysymptomatic porphyria, Thiopental has been shown to worsen symptoms in patients with acute porphyric crisis.
Etomidate is also considered unsafe based on demonstration of its porphyrogenicity in animal models. Ketamine is also considered safe. Propofol is considered safe but continuous infusions should be avoided as there have been reports of elevated porphyrins in patients receiving continuous propofol infusions.

Maintenance:

Volatile agents are generally considered safe. Halothane appears to be the agent of choice and Isoflurane a safe alternative. There is no current data with regards to Sevoflurane and Desflurane, however, the short duration of action of these agents makes them likely to be safe. Enflurane has been shown to be porphyrogenic in animal models but there have been no reports in humans.

Analgesia:

Opiates, acetaminophen, indomethacin and naproxen are considered safe. There is no evidence regarding the use of ketoralac.
Pantazocine and Diclofenac are to be avoided.
Despite the added stress of hypothermia, blood loss and haemolysis during cardiac surgery, sufentanil has reportedly been used safely in Coronary Artery Bypass Surgery.

Muscle relaxants:

Pancuronium and succinylcholine have been used safely. There is little data with regards to rocunium and mivacuronium and should be used with caution, along with atracurium[12] and vecuronium.

Other:

Penicillins, cephalosporins, imipenums and aminoglycosides are safe to use. Patients with porphyria and a penicillin allergy present a challenge and make choice of antibiotic extremely difficult and patients have to be treated on an individual basis depending on severity of infection. Macrocodes, tetracyclines, quinolones and sulphonamides are to be avoided. Metronidazole is also unsafe.

Oxytocin and prostaglandins given intravaginally are safe to use. Ergometrine must be avoided. Tocolytics such as hexaprenaline and atosiban are safe. Prostaglandins use for foetal maturation are safe.

Epilepsy: the drugs that are considered safest for use are: Clonazepam, Lamotrigine and Gabapentin. Phenytoin, phenobarbitone, carbamazepine, valproic acid, topiramate and vigabatrin have been reported to be porphyrinogenic. For immediate termination of seizures: clonazepam and diazepam may be used.

Anti-hypertensives: Diuretics, ACE-inhibitors, ARB blockers and Beta-adrenergic blockers are safe to use in porphyria. As mentioned earlier, beta-adrenergic blockers are anti-porphyrinogenic by decreasing the activity of ALA synthase and are therefore, especially beneficial. Calcium-channel blockers are highly porphyrinogenic in experimental models and should, therefore, be avoided.

PONV: Droperidol and phenothiazines may be used, however odansetron should be used with caution.

Vasopressors: Dopamine and adrenaline are safe to use.

Monitoring:
The use of invasive monitoring should be based on the whether or not the patient is having surgery during an acute crisis, the expected blood loss and duration of the surgery.
Onset of signs and symptoms may occur subtly at first and only develop over 2 to 3 days[(2)] which makes perioperative diagnosis of an acute porphyric crisis difficult especially if the patient does not volunteer a family history of porphyria.
Signs to look out for: autonomic instability (labile blood pressure, tachycardia) intraoperatively and post surgery, delayed emergence, poor respiratory effort even after complete reversal of muscle relaxants and hypnotic agents (secondary to respiratory muscle weakness), flaccid paralysis, seizures, reddish discolouration of urine, postoperative mental state changes and complaints of severe abdominal pain, nausea and vomiting[(14)]. Although these signs and symptoms can occur in a number of other conditions (as mentioned in the list of differential diagnoses previously), it is important to also consider porphyria, especially if all other possible causes have been ruled out

Postoperative Care:
Patients should be monitored for up to a week postoperatively in order to detect the onset of an acute porphyric attack. Changes in blood pressure, new onset of neuropathy or any of the other typical symptoms listed above should alert the clinician to the onset of an acute porphyric crisis.

CONCLUSION

Acute Porphyrias are a group of inherited disorders of haem biosynthesis. Overall they are rare but Variegate Porphyria represents the commonest inherited disorder in South Africa.

The majority of carriers of these enzyme defects will remain asymptomatic throughout their lives. Those who are symptomatic are at risk of developing an Acute Porphyric Crisis which is potentially fatal or may result in irreversible neurological damage.

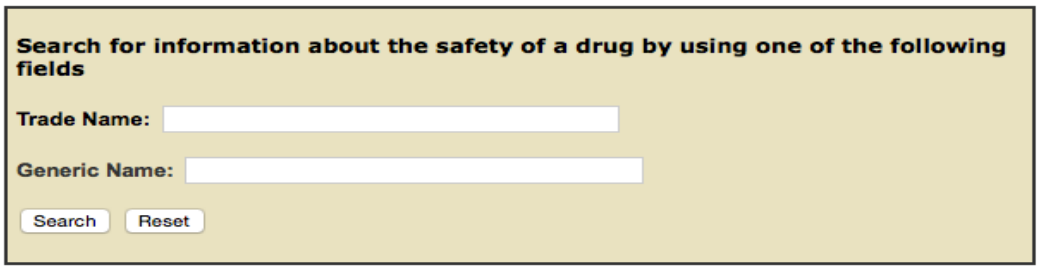
Patients receiving an anaesthetic will be exposed to a vast array of drugs capable of triggering an acute crisis. It is therefore important for anaesthetists to have a clear understanding of the disorder in order to take the necessary precautionary measures.
The development of newer, short-acting anaesthetic agents make delivering a safe anaesthetic technique, possible.

Several drug selection lists and guidelines exist to assist the anaesthetist in providing the best anaesthetic for the type surgery and the patient's individual requirements. There are also several online aids to assist with drug selection if there is uncertainty regarding a drugs safety. One such aid is the Norwegian Porphyria Centre Drug Database for Acute Porphyria:

Key to drug porphyrinogenicity classifications with colour codes and abbreviations used in the database, and advice for prescription:

Drug classifications	Advice for prescription
Not porphyrinogenic (NP)	Used as a first hand choice No precautions needed
Probably not porphyrinogenic (PNP)	Used as a first hand choice No precautions needed
Possibly porphyrinogenic (PSP)	Only used when no safer alternative is available. Precautions motivated in vulnerable patients.
Probably porphyrinogenic (PRP)	Prescribed only on strong or urgent indications. Precautions motivated in all patients.
Porphyrinogenic (P)	Prescribed only on urgent indications. Precautions taken in all patients.
Not yet classified (NC)	Not yet safety classified and should therefore not be used. Prescribed only on strong indication when no safer alternative is available. Seek advice from a porphyria specialist .

Table 3: Drug porphyrinogenicity classifications used in the NAPOS database[11]



It is important to remember, however, that as with most inherited disorders, there is considerable variation between patients and their response to different drugs. It is

therefore, important to look for and rapidly detect the onset of an Acute Porphyric Crisis which can be successfully treated.

Drugs		Recommendation
Inhalational agents	Nitrous oxide	Use
	Cyclopropane	Use
	Halothane	Use
	Enflurane	UWC
	Isoflurane	UWC
	Sevoflurane*	UWC
	Desflurane*	UWC
Intravenous induction agents	Propofol	Use
	Ketamine	UWC
	Barbiturates	Avoid
	Etomidate	Avoid
Analgesics	Acetaminophen	Use
	Alfentanil	Use
	Aspirin	Use
	Buprenorphine	Use
	Codeine	Use
	Fentanyl	Use
	Pethidine (meperidine)	Use
	Morphine	Use
	Naloxone	Use
	Sufentanil	Use
	Diclofenac	UWECO
	Ketorolac*	UWECO
	Phenacetin	UWECO
	Tilidine	UWECO
	Pentazocine	Avoid
Neuromuscular blocking drugs	Tubocurarine	Use
	Pancuronium	Use
	Succinylcholine	Use
	Alcuronium	UWC
	Alcuronium	UWC
	Atracurium	UWC
	Rocuronium*	UWC
	Mivacurium*	UWC
	Vecuronium	UWC
Neuromuscular block reversal agents	Atropine	Use
	Glycopyrrolate	Use
	Neostigmine	Use
Local anaesthetics	Bupivacaine	Use
	Lidocaine	Use
	Prilocaine	Use
	Procaine	Use
	Tetracaine	Use
	Cocaine	UWC
	Mepivacaine	UWC
	Ropivacaine	ND/Avoid
Sedatives and anti-emetics	Domperidone	Use
	Droperidol	Use
	Phenothiazines	Use
	Temazepam	Use
	Triazolam	Use
	Benzodiazepines other than listed	UWC
	Cimetidine	UWC
	Diazepam	UWC
	Lorazepam	UWC
	Metoclopramide	UWC
	Midazolam	UWC
	Ondansetron	UWC
	Oxazepam	UWC
	Ranitidine	UWC
	Chlordiazepoxide	UWECO
	Nitrazepam	UWECO
Cardiovascular drugs	Epinephrine	Use
	Magnesium	Use
	Phentolamine	Use
	Procainamide	Use
	α-Agonists	Use
	β-Blockers	Use
	β-Agonists	Use
	Diltiazem	UWC
	Disopyramide	UWC
	Sodium nitroprusside	UWC
	Verapamil	UWC
	Hydralazine	UWECO
	Nifedipine	UWECO
	Phenoxybenzamine	UWECO

Table 4: Drug List[1]

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