British Journal of Anaesthesia **85 (1)**: 143–53 (2000)

Porphyrias

M. F. M. James* and R. J. Hift

Departments of Anaesthesia and Medicine, University of Cape Town and Groote Schuur Hospital, South Africa

**Corresponding author: Department of Anaesthesia, University of Cape Town Medical School, Anzio Road, Observatory 7925, Cape, South Africa*

Br J Anaesth 2000; **85**: 143–53

Keywords: complications, porphyria; biotransformation (drug); anaesthesia, evaluation, preoperative

The porphyrins play a critical role in biology, being involved in a wide range of reactions related to oxygen utilization, transport, storage or formation. The synthetic pathway involved in the production of the porphyrins is complex and is governed by a sequence of enzymes. A defect in any of these enzymes results in accumulation of the preceding intermediaries and produces one form or another of the diseases known as the porphyrias. This review briefly outlines porphyrin synthesis, the diseases that arise from errors in porphyrin metabolism and the anaesthetic implications of these disorders.

Porphyrin metabolism

The porphyrins are cyclic structures formed by the linkage of four pyrrole rings through methene (–CH=) bridges. The porphyrin ring can, via the nitrogen atom of the pyrrole subunits, form complexes with many metals, giving metalloporphyrins. These compounds are widely distributed throughout the plant and animal kingdoms where they are essential for photosynthesis, oxygen transport, electron transport, the reduction of molecular oxygen and various hydroxylation reactions. Of the metalloporphyrins, the most biologically important are those containing iron (to form haem) and magnesium (to form chlorophyll). The porphyrins are highly coloured and exhibit red fluorescence in ultraviolet light. The porphyrin precursors, the porphyrinogens, which are linked by methyl (CH_2) bridges (Fig. 1), are colourless. When exposed to light and oxygen, they spontaneously convert to porphyrins.

In human physiology, haem is the most important of the porphyrins. In its biologically active form, haem is bound to various proteins to form haemoproteins, which include haemoglobin, myoglobin and all of the cytochromes (including the P_{450} series) together with numerous other compounds involved in oxidation and hydroxylation reactions.

The biosynthesis of haem commences with formation of δ-aminolaevulinic acid (ALA) by the condensation and subsequent decarboxylation of two freely available molecules—succinyl co-enzyme A (succinyl CoA) and the amino acid glycine—in a step catalysed by the enzyme ALA synthetase. This process occurs in the mitochondria (where succinyl CoA is produced in the citric acid cycle); ALA synthetase appears to be the most important rate-limiting enzyme in porphyrin biosynthesis. The next step in porphyrin biosynthesis occurs outside the mitochondria where two molecules of ALA condense under the influence of the enzyme ALA dehydratase to form the monopyrrole subunit of the porphyrin ring, porphobilinogen (PBG). The enzyme PBG deaminase catalyses the condensation of four molecules of PBG to form hydroxymethylbilane, which is then converted into the first of the porphyrinogens, uroporphyrinogen, under the influence of uroporphyrinogen cosynthetase. The stepwise decarboxylation and conversion of uroporphyrinogen acetate groups to methyl substituents results in the formation of coproporphyrinogen which then re-enters the mitochondria where oxidation and chelation with ferrous iron result in the production of haem. These steps together with the relevant enzymes are illustrated in Fig. 2. The porphyrin biosynthetic pathway operates very efficiently and <2% of the porphyrin precursors are produced in excess of that required for haem synthesis. Consequently, the finding of increased concentrations of porphyrin intermediates in urine or stool indicates an abnormality of production, with a partial block somewhere in the enzymatic chain.

Control of haem biosynthesis

The control of the production of haem is effected primarily through ALA synthetase. This enzyme has a low endogenous activity and also has a very short half-life, making it ideally suited to a regulatory role. The formation of ALA

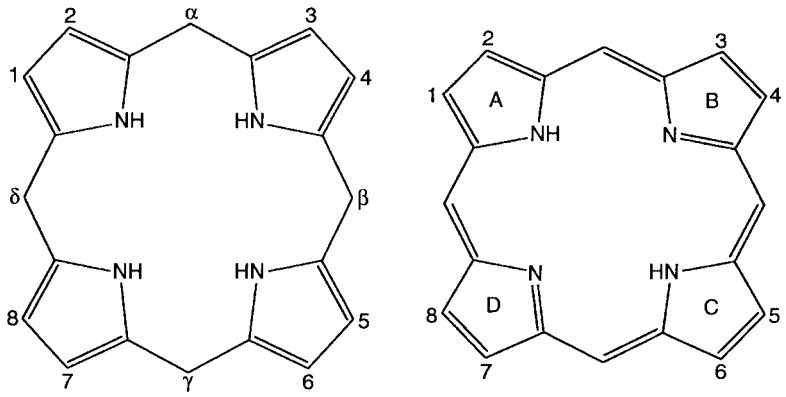

Fig 1 The structures of the porphyrinogens (left) and porphyrins (right). Substituents are numbered according to the conventional Fisher system. In the porphyrinogen ring, the positions designated by Greek letters are occupied by methyl groups ($-CH_2$), whereas in the porphyrin ring these positions are occupied by methene (–CH=) groups. The colourless porphyrinogens undergo spontaneous conversion to purple-coloured porphyrins on exposure to light and air, hence the characteristic urine colour change, when urinary porphyrinogens are present, from normal to a 'port wine' appearance on standing.

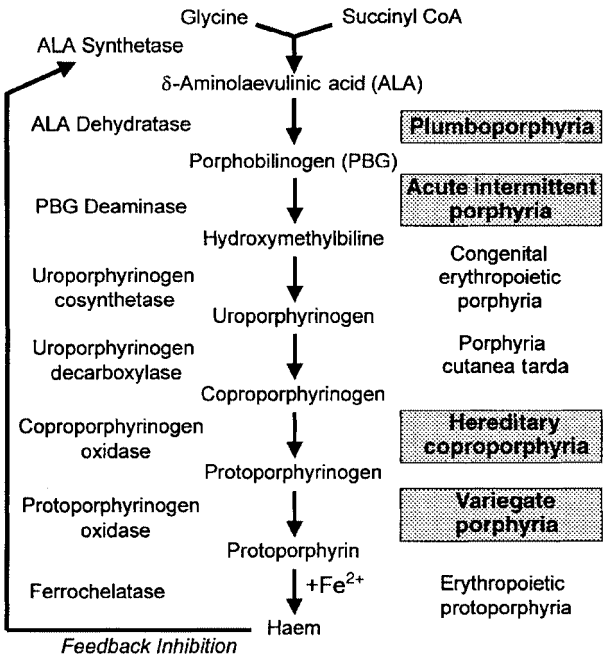

Fig 2 Metabolic pathways of haem synthesis. The enzymes involved at each step are listed on the left, and the type of porphyria associated with a deficiency of each enzyme is shown on the right. The conditions highlighted in boxes are the acute porphyrias.

synthetase is controlled by the concentration of haem itself, which forms a negative feedback loop, thus ensuring that the level of haem production matches requirements closely. The concentration of haem required to suppress enzyme *production* is extremely low, of the order of 10^{-7} M, while that required to inhibit enzyme *activity* is of the order of 10^{-5} M. However, the concentration of haem generated within the mitochondrion is insufficient to inhibit the enzyme, so ALA synthetase control is thought to be exerted by a volatile 'free haem pool' within the cytosol.[38] It is also possible that some measure of control is exerted by the availability of glycine.

ALA synthetase is readily inducible and can respond rapidly to increased haem requirements such as those resulting from the administration of drugs which require cytochrome P_{450} for their metabolism. Thus the availability and activity of the enzyme depend on the intracellular level of haem, and the demand for haem by metabolic processes. This fact is of great relevance in the development of the porphyrias, in which an increase in haem requirements in the face of a partial block in the synthetic pathway results in the overproduction of ALA synthetase, and consequently of the pathway intermediates before the block. The enzyme PBG deaminase also seems to have a regulatory role that is of relevance in some porphyric conditions. Under normal circumstances, an increase in production of ALA results in an increase in activity of PBG deaminase, thus enabling the synthetic pathway to continue efficiently. However, in acute forms of the disease, there appears to be a concomitant failure of PBG deaminase to respond appropriately, with a resultant accumulation of the early components of the metabolic pathway. Recent work has shown that coproporphyrinogen and protoporphyrinogen, both of which are produced in excess in variegate porphyria, can also inhibit PBG deaminase.[34]

Classification of the porphyrias

The porphyrias can be classified by the main site of the defect (hepatic or erythropoietic), by the enzyme defect (Fig. 2) or by whether or not they cause acute symptoms (Table 1). The latter method of classification is particularly useful for anaesthetic practice as only the acute forms of the porphyrias are of major anaesthetic relevance, since these are the conditions that may result in life-threatening reactions to drugs. All the hepatic porphyrias except for porphyria cutanea tarda are acute porphyrias.

Table 1 Classification of the porphyrias

Type of porphyria	Examples
Acute	acute intermittent porphyria (AIP); variegate porphyria (VP); hereditary coproporphyria (HC); plumboporphyria (PP)
Non-acute	porphyria cutanea tarda (PCT); erythropoietic porphyrias: congenital erythropoietic porphyria (CEP); erythropoietic protoporphyria (EPP)

The acute porphyrias

The acute porphyrias include acute intermittent porphyria (AIP), variegate porphyria (VP), hereditary coproporphyria (HCP) and the very rare plumboporphyria (PP). With the exception of PP, which is recessive, these porphyrias are inherited as non-sex-linked, autosomal dominant conditions with variable expression. Like many inherited conditions, they have a patchy distribution. The overall frequency of AIP in Europe is estimated to be one per 20 000, with one per 10 000 in Northern Sweden and an even higher incidence in Lapland. VP is particularly common in the Afrikaner community in South Africa where the prevalence has been estimated at between one in 250 and one in 500,[12] but the disease is recognized worldwide and in Britain is thought to be about a third as prevalent as AIP.[17] The true incidence of these conditions is hard to estimate as many individuals remain asymptomatic throughout their lives; this is particularly true of HCP where more than half the affected individuals may be symptom-free.

The enzyme defects in porphyria are deficiencies rather than absolute deficits. In most patients with clinically expressed porphyria, the level of enzyme reduction is generally of the order of 50%,[26] suggesting that the defective allele produces essentially no enzyme activity. This may be why homozygotes are extremely rare, as complete failure to produce haem is probably incompatible with life. Increasingly, however, families are being identified in which mutations appear to encode proteins with some residual activity. Where such a family marries into another carrying a more typical mutation for the same defect, compound heterozygotes may result; such patients express low levels of enzyme and characteristically are phenotypically severely affected. Although there is no direct influence of gender on the pattern of inheritance, attacks occur more frequently in women and are most frequent in the third and fourth decades. Few cases have been reported before puberty, and attacks are rare after the menopause,[29] although presentation has occurred between the ages of 7 and 75 yr.[27] Acute attacks of porphyria are most commonly precipitated by events that decrease haem concentrations, thus increasing the activity of ALA synthetase and stimulating the production of porphyrinogens. Acute exacerbations may be precipitated by a number of factors, including physiological hormonal fluctuations (such as those occurring with menstruation), fasting, dehydration, stress and infection.[14] Though pregnancy was thought to represent a particular risk in the porphyric patient, with acute attacks reportedly occurring in a high proportion of pregnant patients (24–95%) with AIP,[29] more recent experience suggests that the rate in pregnancy is lower. Frequent spontaneous abortion (6–12%) and hypertension may, however, complicate pregnancy in the patient with AIP and there is an increased incidence of low-birthweight infants. Nevertheless, enzyme-inducing drugs are by far the most important trigger factors, particularly in relation to anaesthesia.

Acute attacks are characterized by severe abdominal pain, autonomic instability, electrolyte disturbances and neuropsychiatric manifestations; they may range from a mild disturbance to fulminating attacks with a fatal outcome.[17] Neuromuscular weakness, which may progress to quadriparesis and respiratory failure, is the most prominent and potentially lethal neurological manifestation, but sensory losses also occur. Central nervous system involvement with upper motor neuron lesions, cranial nerve palsies and involvement of the cerebellum and basal ganglia are less commonly seen. Permanent neurological lesions, especially parasympathetic dysfunction, can occur, particularly in AIP, although this is rarely seen unless the attacks have been multiple or of long duration. Though psychiatric disturbances were believed to occur in a high percentage of overt sufferers from the condition, the current belief is that these have been greatly exaggerated. Seizures may occur during an acute attack. Gastrointestinal symptoms are the most common and typically present with severe abdominal pain with vomiting and occasionally diarrhoea. Clinical examination of the abdomen is remarkably normal considering the severity of the symptoms,[15] since there is no peritonism. Abdominal pain is thought to relate directly to the autonomic neuropathy, though there may be a contribution from abnormal bowel function with alternating areas of spastic and relaxed bowel. Ganglionic blockade may, therefore, be helpful in this condition,[6] though it is seldom necessary, since the abdominal complaints commonly abate promptly with resolution of the attack. Dehydration and electrolyte abnormalities of Na^+, K^+ and Mg^{2+} may be severe and careful fluid and electrolyte management is essential. Cardiovascular instability—with tachycardia and arterial pressure changes of hypertension or, less commonly, hypotension—occurs, particularly in AIP, and permanent hypertension may result.

Between attacks, complete remission is the norm, and many subjects with the genetic defect remain asymptomatic. This is particularly important when planning a drug regimen in patients potentially at risk, as patients with so-called

'silent' (or latent) porphyria may have their first symptoms precipitated by injudicious administration of triggering agents. In all the acute porphyrias, acute attacks are characterized by markedly increased concentrations of ALA and PBG in the urine, though in PP the elevation is limited to ALA since the enzyme defect here lies before the step in which PBG is synthesized.

Drugs may trigger an acute attack of porphyria in many ways, most of which depend on an increased demand for haem production or a failure of haem inhibitory feedback as the final common pathway. Thus drugs may induce the transcription of ALA synthetase directly through mRNA or may interfere with the negative feedback control which haem exerts on ALA synthetase production. Drugs may interfere with the haem synthetic pathway, thus reducing the level of haem production, or they may increase the demand for haem by increasing utilization, for example through increased demand for oxidative processes mediated through the cytochromes. This multitude of potential pathways and the great variety of drug structures make it impossible to predict which agents are likely to be porphyrinogenic. The only properties of drugs which are clearly linked to porphyrinogenicity are lipid solubility[11] and membrane fluidization.[42] Some chemical groupings, such as the allyl groups which form the basis of the barbiturates, and certain steroid structures have also been incriminated in the induction of porphyria (steroids can enhance the induction of ALA synthetase). It is of interest that it is only the acute forms of the disease that are affected by enzyme induction, so this is the only form of the disease of pharmacogenetic importance. It is not clear why the manifestations of the non-acute forms of porphyria are not apparently affected by enzyme-inducing drugs. Even such potent inducers of ALA synthetase as the anticonvulsants do not exacerbate or precipitate porphyria cutanea tarda (PCT) or the erythropoietic porphyrias. The only apparent drug association with PCT is that of oestrogen-containing compounds. They may exacerbate the biochemical and skin manifestations of this condition, but acute attacks are never encountered in PCT. There are occasional reports of other agents being implicated in either the causation or exacerbation of the non-acute porphyrias, but Moore and colleagues concluded that the evidence for induction of these conditions by drugs other than oestrogens is weak.[38]. These conditions will, therefore, not be considered further. For more information about the non-acute porphyrias, see the review by Paslin.[45] Notably, there is no excess excretion of ALA or PBG in these conditions, whereas these changes are the hallmarks of the acute porphyrias.

The pathogenesis of the acute porphyrias is unclear, although there are several possibilities. The excessive production of ALA is common to all of the acute forms and in all but the very rare plumboporphyria there is a defect in PBG deaminase, either in terms of an absolute reduction of enzyme activity, or in terms of a failure to increase its level in response to increased demand. Thus it is possible that ALA or PBG, or both, may be directly neurotoxic, although the severity of the symptoms does not correlate well with the increase in either of these substances. Nevertheless, the accumulation of these two compounds appears likely to have some effect on symptomatology. An alternative, but not exclusive, hypothesis is that the failure of haem production results in an acute haem deficiency within the nerve cell, and that this is the chief cause of the neuronal lesions, although the toxicity of ALA and PBG may still be relevant.[38] It has also been suggested that haem deficiency results in a secondary reduction in the activity of haem-containing enzymes such as tryptophan oxygenase, with consequent disturbances in the production and metabolism of potential neurotransmitters such as serotonin.

Acute intermittent porphyria

The defective enzyme in this condition is porphobilinogen deaminase and the gene encoding this enzyme is located on chromosome 11. PBG deaminase deficiency can, in most cases, be detected in red cells between attacks. Of all the porphyrias, this one produces the most severe symptoms, and is the one in which an acute attack is most likely to be fatal. It has been reported that hypertension and impaired renal function are significantly more common in porphyric subjects than in their non-porphyric relatives, and that hypertensive complications and renal failure are the most frequent causes of death in patients with porphyria.[9]

Variegate porphyria

This condition is characterized by cutaneous photosensitivity in which bullous skin eruptions occur on exposure to sunlight as a result of the conversion of porphyrinogens to porphyrins. The characteristic skin lesion is one of excessive fragility, especially on sun-exposed surfaces such as the face and hands, where bullae and erosions with subsequent pigmented 'tissue paper' scarring are frequently seen. The name of this condition derives from the fact that patients may present with the skin manifestations associated with the non-acute porphyrias, or the disorders characteristic of AIP or combinations of both. The enzyme defect is at the level of protoporphyrinogen oxidase but there is also a reduced amount of PBG deaminase. The gene encoding this enzyme is on chromosome 1. The incidence of VP in South Africa is the highest in the world: in some areas it may be as high as one in 250 of the white population.[12] This has been shown to result from the introduction of a single point-mutation by a Dutch settler in 1688.[35]

Hereditary coproporphyria

This condition is far less common than VP and AIP. Acute attacks appear to be considerably less severe, and the prognosis better. The defective enzyme is coproporphyrino-

Table 2 Summary of major biochemical findings in the acute porphyrias. Note that the findings described in the quiescent phase apply only to those with biochemically expressed disease; silent carriers will demonstrate no abnormality on urine and faecal testing, yet carry the gene and are at risk of an acute attack

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

gen oxidase, encoded by a gene on chromosome 9. As in VP, cutaneous photosensitivity is characteristic, though it tends to be less severe in the interval between acute attacks than it is in VP.

Plumboporphyria

This, the rarest of the acute porphyrias, results from a deficiency of ALA dehydratase, which is encoded by a gene on chromosome 9. It is associated with an excess of urinary ALA analogous to that found in lead poisoning (hence the name), although lead concentrations in the blood are normal. Unlike the other acute porphyrias, the mutation is recessive, and the disease presents early in life, with all clinically manifest cases being homozygotes.[19] No references to anaesthesia for patients with this condition have been published.

Implications for anaesthesia

It might be expected that the cytochrome-mediated metabolism and high lipid solubility of many anaesthetics would make many of them porphyrinogenic, and anaesthesia has certainly been implicated in the triggering of a number of severe porphyric reactions. Nevertheless, most porphyrics can be anaesthetized with relative safety provided that appropriate precautions are taken. The mainstay of safe anaesthetic management of the porphyric patient depends on the detection of susceptible individuals, and the identification of potentially porphyrinogenic agents. Neither of these is simple or readily achievable.

Identification of susceptible individuals

Laboratory identification of porphyric subjects is not easy, as many of them show only subtle or even no biochemical abnormalities during asymptomatic phases. The identification of potentially porphyric patients must, therefore, begin with knowledge of the local prevalence of the condition and then rely on the recognition of a suggestive personal or family history. Any suggestion of porphyria in the patient's history should be taken seriously and appropriate laboratory investigations undertaken. Where the urgency of the situation precludes full biochemical evaluation, the patient should be managed with an anaesthetic technique appropriate for a porphyric patient. The most appropriate test for the diagnosis of porphyria will vary according to the type of porphyria expected and the patient's circumstances. Thus, when the actual mutation is known in the family, DNA analysis is most appropriate. In the absence of this knowledge, determination of erythrocyte PBG activity is probably the most appropriate screening test for patients with suspected AIP, as detection of elevated ALA and PBG in urine is less sensitive. In the case of possible VP, HCP or a suspected acute attack, biochemical analysis of urine, stool and plasma porphyrin profiles is indicated. Direct enzyme activity estimates are problematic in these patients, because activity is expressed not in erythrocytes but only in nucleated cells such as fibroblasts or leukocytes, and then in such low amounts that standard assays are unreliable. The biochemical tests vary in their ability to identify porphyric patients depending on the type of the condition and whether or not the individual is in remission or suffering an attack; their interpretation is listed in Table 2. It must be remembered that prepubertal children who carry the gene will be asymptomatic, but are still at risk from an acute attack if improperly managed.[45]

Identification of drugs

The identification of drugs likely to be hazardous to the porphyric patient is also far from clear-cut. The labelling of drugs as safe or unsafe in porphyria is based on anecdotal experience of the use of the agents in porphyric patients and reports of the induction of acute attacks, or on measurements of porphyrins or their precursors in urine or faeces. Drugs may be tested for in cell culture models for their ability to induce ALA synthetase activity or for effects on porphyrin synthesis. Alternatively, their actions on the porphyrin synthetic pathway in animal models of porphyria can be investigated; in these models, porphyria is mimicked by administering known porphyrinogenic agents, such as the enzyme-blocking drug dicarbethoxy-dihydrocollidine (DDC). Both cell culture and animal models tend to overestimate the porphyrinogenicity of drugs. A summary of anaesthetic drugs for their perceived safety has been published previously.[22] However, as there are often conflicting reports of the safety of anaesthetic drugs in clinical

Table 3 Recommendations applied to drugs in the Porphyria Drug Safety Database

Category	Description
Use	The drug is likely to be safe and may be used freely.
Use with caution (UWC)	Though safety is not established beyond doubt, the evidence suggests that the drug is unlikely to prove unsafe in practice. It may be used provided no safer alternative is available or suitable.
Use with extreme caution only (UWECO)	There is evidence to suggest that the drug may yet prove unsafe in practice, or grounds to suspect this may be so, or too little evidence to suggest that it may be safe. Such drugs should only be used if the expected benefits strongly outweigh the risks, and an adverse outcome must be anticipated.
Avoid	There is evidence that such drugs have precipitated acute attacks in patients, or other grounds for believing that the risk of an acute attack is high.
No data/avoid (ND/avoid)	There is too little evidence to draw a conclusion, and it is wisest to regard the drug as potentially hazardous and avoid its use.

practice, and since other factors such as infection or stress may precipitate a porphyric crisis coincidentally with the administration of anaesthesia, it is extremely difficult to assess the porphyrinogenic potential of anaesthetic agents with precision. Thus, any attempted classification of anaesthetic agents with regard to their porphyrinogenicity is far from ideal, and inevitably somewhat arbitrary.

In view of the difficulties clinicians experience in interpreting such terms as 'possibly safe' and 'probably unsafe' in drug lists, the Porphyria Drug Safety Database held at the University of Cape Town has been reviewed and modified to reflect the terms listed in Table 3, which give a clearer indication of the relative desirability of drugs. Those drugs most applicable to anaesthesia are listed in Table 4. The information presented in this table was obtained by examining data from the literature (itself based on clinical experience as well as animal and *in vitro* experiments), from personal experience and by the examination of drugs for structure, structural similarity and routes of metabolism. As such it represents both compromise and intuition unsubstantiated by hard data, and the recommendations cannot be guaranteed to prove valid under all circumstances. The list should serve as a guide only, and the authors cannot accept responsibility for errors or for any adverse experience. More information on specific agents may be obtained from the authors.

In general, drugs should be selected in the order Use, UWC, UWECO, ND/avoid and Avoid. Particular care must be taken when prescribing drugs for patients with AIP or clinically active forms of porphyria and when prescribing drugs in combination. Aggravation of porphyria is more likely under these circumstances.

Anaesthetic management

Any patient in whom porphyria is suspected requires a careful history, including a detailed family history, and thorough physical examination, including a careful neurological assessment, paying particular attention to the presence or absence of peripheral neuropathy and autonomic instability.[1] Note, however, that in the vast majority of patients, there will be no clinical evidence of the disease other than possible skin lesions (which are often subtle) in those with VP and, in the rare patient who has had previous acute attacks, some evidence of neuropathy.

If an acute crisis is suspected, particular attention must be paid to muscle strength and cranial nerve function, as symptoms related to these areas may predict impending respiratory failure or an increased risk of aspiration. Cardiovascular examination may reveal hypertension and tachycardia; these should be treated before anaesthesia. Respiratory muscle function may be compromised, and respiratory function tests may be indicated. In an acute crisis, postoperative ventilation may be required. During an acute exacerbation, the possibility of non-surgical abdominal pathology must always be suspected, with a high index of suspicion in a patient in whom the severity of symptoms is not matched by clinical findings. Preoperative preparation in a patient with an acute porphyric crisis must include the careful assessment of fluid balance and electrolyte status.

Premedication

Most (but not all) benzodiazepines commonly used for premedication are considered safe. The phenothiazines may have particular advantages. Good anxiolysis has been recommended as advantageous.[1] Where antacid administration is considered appropriate, sodium citrate may be given and ranitidine may be considered. Cimetidine has been recommended in the treatment of acute porphyric crises, since it may decrease haem consumption and inhibit ALA synthetase activity.[27] However, although it may be used safely as an H_2 receptor antagonist, it does not appear to be effective prophylactic therapy.[27] Preoperative starvation should be minimized; if a prolonged fast is unavoidable, a dextrose–saline infusion should be given during the preoperative period, since calorie restriction has been linked with the precipitation of acute attacks. In view of the frequency with which hyponatraemia is encountered in acute attacks, intravenous fluids containing dextrose alone should be avoided.

Regional anaesthesia

There is no absolute contraindication to the use of regional anaesthesia in the porphyric patient. However, careful

examination and evaluation of the neurological status of the patient before the performance of a regional block is essential. Cardiovascular stability may be compromised by hypovolaemia and autonomic neuropathy.

Theoretically, lidocaine, which has been shown to be potentially porphyrinogenic in both of the commonly used animal models, should be considered unsafe. However, wide experience with the agent has not shown significant problems either when used as a local anaesthetic or when used intravenously for the control of arrhythmias, although experience with the latter usage is limited. On the basis that a worsening of the neuropathy might be ascribed to epidural anaesthesia, fear of litigation has been raised as an argument against the use of regional blockade.[26] However, as there is no evidence that any local anaesthetics have ever induced an acute attack or neurological pathology in porphyric subjects, there seems no good reason to avoid their use. This view is supported by a report of two instances of the use of regional anaesthesia in AIP during pregnancy in both of which bupivacaine (one epidural and one spinal administration) was used without complication.[32] The authors concluded that there was no evidence that general anaesthesia was safer for the pregnant porphyric patient than regional anaesthesia. In theory, procaine is the best agent to use, but in practice bupivacaine appears to be safe, and the intrathecal route, in which a minimum of agent is injected, seems ideal. The epidural use of procaine and fentanyl in a pregnant porphyric patient has been reported.[28] Böhrer and Schmidt[4] reported two cases managed with local anaesthesia and concluded that regional or local anaesthesia with bupivacaine, prilocaine, tetracaine or procaine may be the technique of choice for porphyric patients whenever the technique was applicable. However, problems with haemodynamic instability, mental confusion and associated neuropathy probably preclude the use of regional anaesthesia in the presence of an acute porphyric crisis,[1 27] although there are no studies specific to this issue.

General anaesthesia

The total dose of drug administered and the length of time for which the patient is exposed to the drug may influence the probability of triggering a porphyric crisis. The current availability of very short-acting anaesthetic agents almost certainly contributes to the increased safety of most modern anaesthetic techniques, although there are still some areas of controversy.

Induction. The barbiturates are the archetypal inducers of ALA synthetase, and all barbiturates, including thiopental, must be considered unsafe. Although there are numerous reports of the safe use of thiopental in porphyric patients in the quiescent phase,[53] seven out of 10 patients in acute porphyric crisis had their symptoms worsened following induction of anaesthesia with thiopental.[40] Thus, although thiopental will not always precipitate a crisis, all barbiturates must be considered contraindicated in porphyric patients. Etomidate is potentially porphyrinogenic in animal models[23] and at least one crisis has followed its use in human subjects, although its safe use has also been reported;[18] on balance, etomidate should probably be considered unsafe. Ketamine is probably safe; it has been used safely in quiescent AIP;[2 47 52] its safe use during a crisis in HCP has been reported,[7] and most animal and cell culture models suggest that it is non-inducing. However, an increase in ALA, PBG and other porphyrins after ketamine has been reported in a patient in the latent phase of AIP, and it would seem wise to reserve ketamine for use where haemodynamic or other considerations make it the drug of choice. The use of propofol in porphyria is also contentious to some degree. Animal data are conflicting; there is no evidence of porphyrinogenicity in the DDC-primed rat, but some evidence of induction of ALA synthetase in the chick embryo.[13] There are many case reports of patients with AIP[8 10 25 29 31 37 46 50 58] and HCP[48] and a prospective study of patients with VP[36] who received propofol safely. Although there are two reports of elevated porphyrins following propofol anaesthesia in patients with VP[59] and AIP,[16] continuous infusions of propofol were used in both cases and total doses of 900 or 1300 mg were administered; neither patient had any porphyric symptoms following the use of propofol. On balance, therefore, it appears that propofol can safely be used for induction of anaesthesia, although a question mark must remain against its use as a continuous infusion.

Inhalational agents. Nitrous oxide is well established as safe and cyclopropane and ether are also thought to be without risk. Halothane has been used in many cases of porphyria and is generally regarded as safe. There are two cases of a possible hazard attributed to halothane supported by some experimental evidence.[22] However, in view of other experimental data which do not support this view, together with extensive clinical experience of its use, halothane may be listed as safe.[22] This is particularly important as the status of the other two main potent inhalational agents, enflurane and isoflurane, is less certain. Safe use of isoflurane has been reported[5 6 29–31] and there appear to be no reports of adverse effects. Isoflurane should probably, therefore, be classified as safe, although further information needs to be obtained. Enflurane has been shown to induce porphyrin synthesis in animal models[5 43] but has been used safely in patients. There are few reports of its use, but there seems no absolute contraindication to enflurane in porphyric patients. There are no published data relating to sevoflurane or desflurane, although the short duration of action of both agents, and the minimal metabolism of the latter, make them likely to be safe. On balance, halothane would appear to be the current agent of choice, and isoflurane may be a satisfactory alternative; none of the other newer halogenated hydrocarbons are as yet absolutely contraindicated, though caution should be exercised in view of the very limited experience with their use in porphyric patients.

Neuromuscular blocking drugs. Succinylcholine has been used for many years and has been proven to be safe, as has tubocurarine. Though both pancuronium and alcuronium have been classified as unsafe by some authors, they have been widely used by many anaesthetists without harm. Atracurium[6 29 30] and vecuronium[31] have been used safely in small numbers of patients despite some experimental evidence for porphyrinogenicity. There would appear to be little to choose between these various agents; by analogy, mivacurium and rocuronium too are unlikely to prove dangerous, though there are no published data on their safety. Caution should, however, be exercised, particularly where extended use is intended, for example in the patient in the intensive care unit undergoing prolonged ventilation. As with propofol, prolonged use may not be safe, whereas a single dose may be.

Analgesic agents. Morphine and its analogues (including codeine) are of proven safety, and fentanyl has been shown to be safe both in chick embryo culture models and in clinical use. Alfentanil has also been used frequently with no reported complications. More recently, fentanyl[55] and sufentanil[54] have been used as a major component, in combination with isoflurane and atracurium, in open heart surgery without problems.[6] These cardiac surgical reports also refer to the safe use of heparin. Pethidine (meperidine) has a proven track record of safety despite a single case report implicating it in a porphyric attack.[14] Pentazocine and tilidine have been listed by several authors as unsafe, though the reasons for this are unclear. There is evidence both for[44] and against[13] the porphyrinogenicity of pentazocine in experimental systems. Of the non-opiate analgesics, aspirin, acetaminophen, indomethacin and naproxen have proven safe. Disler and Moore[14] recommend the avoidance of the pyrazalone derivatives (such as phenylbutazone), the anthranic acid derivatives (such as ibuprofen and fenoprofen) and diclofenac. There is no information regarding ketorolac.

Cardiopulmonary bypass is a specific problem, as the additional stress imposed by hypothermia, the haemolysis induced by the bypass pump, blood loss and the large number of pharmacological agents that need to be administered may all worsen the risk of development of a porphyric crisis. However, there are several reports of the safe performance of cardiac surgery in porphyric patients provided that appropriate drug regimens are selected.[49 51 54 55] Blood loss, with its consequent increase in haem demand by the bone marrow, does not appear to stress the haem synthetic pathway sufficiently to provoke a porphyric crisis.[20]

Guidelines for selecting drugs for anaesthesia in patients with porphyria

No cases of anaesthesia-induced porphyric crisis have been reported to the national porphyria referral centre at Groote Schuur Hospital in the last 20 years. This is probably not only the result of improved patient screening and careful drug selection; we believe that in many instances drugs of unproven safety or even those which are known to aggravate porphyria have been administered. The following factors are relevant, and will be taken into account by the prudent anaesthetist.

(i) There is evidence that single exposures to potent inducers, such as thiopental, are often tolerated, but that exposure in patients whose porphyria is already induced is dangerous.[40] It seems likely that the risk with modern, short-acting anaesthetic agents is low, possibly because their rapid elimination means that exposure time is not long enough for significant enzyme induction to occur. Repeated or prolonged exposure may, however, be dangerous, as may be the case with propofol described above.

(ii) There is reason to believe that exposure to multiple potential inducing agents may be far more dangerous than exposure to any one drug.

(iii) Some of the drugs traditionally listed as unsafe on the basis of animal or cell culture experiments may not, in practice, be unsafe.

(iv) Case reports reporting adverse outcomes are frequently unreliable. They may be written by clinicians inexperienced in the interpretation of porphyrin biochemical data; sometimes this amounts to blatant ignorance, as when drug outcomes are reported in patients with PCT, which is not an acute porphyria.

This has led to the more recent, lenient approach to recommendations for drug administration reflected in Table 4 and in the paragraphs above. However, a more relaxed approach is under no circumstances to be confused with a careless or unthinking approach. Every patient must be assessed individually. In particular, patients with evidence of more active porphyria or a history of acute attacks, particularly of AIP, and prolonged administration of drugs not known unequivocally to be safe, or their sequential or concomitant use, provide fertile ground for the precipitation of an attack.

Inadvertent use of porphyrinogenic drugs

If a porphyric patient is given a triggering agent, either because of failure to detect the porphyric status of the patient, or by simple human error, a number of steps have been recommended.[21] No specific prophylactic therapy is available, but since carbohydrate loading can suppress porphyrin synthesis, it is recommended that oral carbohydrate supplements should be given with a target of 200 kcal 24 h^{-1}. If oral feeding is impossible, a 10% dextrose–saline infusion should be given. Haematin, which is the most effective therapy for an acute attack, has not been evaluated as a prophylactic, but should be available and administered promptly if an attack occurs. The patient should be

Table 4 Recommendations for the use of anaesthetic drugs in the acute porphyrias (adapted from ref. 24). The terms used for the recommendations are explained in Table 3, and should be read in conjunction with the text. *There are no published data on these drugs; their recommendations are based on a comparison with drugs of the same class

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
	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

monitored carefully with urine sampling for porphyrins for at least 5 days and supportive therapy given if necessary.

Should an acute attack occur, the first step in management is to ensure that any possibly precipitating factors are withdrawn. Adequate hydration and carbohydrate intake must be ensured in the face of the nausea and vomiting which accompanies the acute attack; use of a nasogastric tube may be necessary. Pain often requires opiates in high and frequent doses. Sedation with phenothiazines may assist by encouraging sleep, which has been reported to diminish the pain, but is usually unnecessary when sufficient doses of opiate have been given. Nausea and vomiting will respond to the phenothiazines, and ondansetron may be useful if extrapyramidal side-effects occur, although its use in this setting has not been described. Beta-adrenergic blockers may be valuable in controlling tachycardia and hypertension, and may also decrease the activity of ALA synthetase. Fluid balance and electrolyte disturbances must be managed aggressively. Magnesium sulphate infusions may be useful in the management of crises associated with magnesium deficiency.[56] Should convulsions occur, the traditional anticonvulsants are, of course, largely contra-indicated, but diazepam and clonazepam may be used. Haematin is the only specific form of therapy; it is thought that it supplements the intracellular free haem pool, thus repressing ALA synthetase. This agent, together with advice on its use, is usually available from expert centres specializing in porphyria. However, it is unstable and can cause renal failure, thrombophlebitis and dose-related coagulopathy.[1 3 39] Haem arginate is more stable and does not have the adverse effects attributed to haematin.[41] It may be preferable to haematin.[57] Somatostatin decreases the rate of formation of ALA synthetase and, together with plasmapheresis, has been used successfully to reduce pain and produce complete remission of symptoms in seven porphyric patients with acute exacerbations.[33]

Conclusions

The acute porphyrias are rare but they are important in anaesthesia because of the wide range of agents that can trigger an acute crisis. The recent appearance of pharmacological agents with short half-lives and the availability of a wide range of anaesthetic drugs that are almost certainly safe in the patient with acute porphyria have markedly reduced the dangers associated with anaesthesia in these patients. Consequently, provided that reasonable precautions are adopted, and sensible guidelines followed, anaesthesia for porphyric patients should not prove unduly hazardous.

The simplest course for the practising anaesthetist to adopt is not to attempt to remember a large range of drugs that are potentially hazardous, but rather to develop a simple, safe technique based on agents that have minimal risk of triggering a porphyric crisis. On the basis of the literature reviewed in this article, it would appear that propofol is now the induction agent of choice, although ketamine may be used if required. Most muscle relaxants appear to be reasonably safe, and all of the inhalational agents, with the possible exception of enflurane, can probably be used. Analgesia can be provided with any of the opiates currently in use, though tilidine and pentazocine should be avoided and care should be taken in choosing a non-steroidal anti-inflammatory agent. Regional anaesthesia, with any of the currently available agents, is not contraindicated and may be of benefit where appropriate. There is thus a more than adequate range of pharmacological agents available for use in the porphyric patient. The choice of agent may be based more on the patient's anaesthetic and surgical requirements, rather than governed by the specific requirements imposed by porphyria.

References

1 Ashley EM. Anaesthesia for porphyria. *Br J Hosp Med* 1996; **56**: 37–42

2 Bancroft GH, Lauria JI. Ketamine induction for cesarean section in a patient with acute intermittent porphyria and achondroplastic dwarfism. *Anesthesiology* 1983; **59**: 143–4

3 Bissell DM. Treatment of acute hepatic porphyria with hematin. *J Hepatol* 1988; **6**: 1–7

4 Böhrer H, Schmidt H. Regional anesthesia as anesthetic technique of choice in acute hepatic porphyria. *J Clin Anesth* 1992; **4**: 259

5 Buzaleh AM, Enriquez de Salamanca R, Batlle AM. Porphyrinogenic properties of the anesthetic enflurane. *Gen Pharmacol* 1992; **23**: 665–69

6 Campos JH, Stein DK, Michel MK, Moyers JR. Anesthesia for aortic valve replacement in a patient with acute intermittent porphyria. *J Cardiothorac Vasc Anesth* 1991; **5**: 258–61

7 Capouet V, Dernovoi B, Azagra JS. Induction of anaesthesia with ketamine during an acute crisis of hereditary coproporphyria. *Can J Anaesth* 1987; **34**: 388–90

8 Christian AS. Safe use of propofol in a child with acute intermittent porphyria. *Anaesthesia* 1991; **46**: 423–24

9 Church SE, McColl KE, Moore MR, Youngs GR. Hypertension and renal impairment as complications of acute porphyria. *Nephrol Dialysis Transplant* 1992; **7**: 986–90

10 Cooper R. Anaesthesia for porphyria using propofol. *Anaesthesia* 1988; **43**: 611

11 De Matteis F, Aldridge WN. *Haem and Haemoproteins*, Berlin: Springer-Verlag, 1978

12 Dean G. *The Porphyrias: A Story of Inheritance and Environment*, 2nd edn. Bristol: Pitman Medical, 1971

13 Deybach JC, Da Silva V, Phung LN, Levy JC, Nordmann Y. Drug risk of hepatic porphyria. Development of an animal experiment model. *Presse Med* 1987; **16**: 68–71

14 Disler PB, Moore MR. Drug therapy in the acute porphyrias. *Clin Dermatol* 1985; **3**: 112–24

15 Eales L, Day RS, Blekkenhorst GH. The clinical and biochemical features of variegate porphyria: an analysis of 300 cases studied at Groote Schuur Hospital, Cape Town. *Int J Biochem* 1980; **12**: 837–53

16 Elcock D, Norris A. Elevated porphyrins following propofol anaesthesia in acute intermittent porphyria. *Anaesthesia* 1994; **49**: 957–58

17 Elder GH, Hift RJ, Meissner PN. The acute porphyrias. *Lancet* 1997; **349**: 1613–17

18 Famewo CE. Induction of anaesthesia with etomidate in a patient with acute intermittent porphyria. *Can Anaesth Soc J* 1985; **32**: 171–3

19 Goldberg A, Moore MR, McColl KE, Brody MJ. Porphyrin metabolism and the porphyrias. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. *Oxford Textbook of Medicine,* 2nd edn. Oxford: Oxford University Press, 1987; 9.136–9.145

20 Harper P, Hybinette T, Thunell S. Large phlebotomy in variegate porphyria. *J Int Med* 1997; **242**: 255–59

21 Harrison GG. Propofol anaesthesia in pharmacogenetic states. In: Rawlinson E, ed. *Focus on Infusion*. London: Current Medical Literature, 1991

22 Harrison GG, Meissner PN, Hift RJ. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48**: 417–21

23 Harrison GG, Moore MR, Meissner PN. Porphyrinogenicity of etomidate and ketamine as continuous infusions. Screening in the DDC-primed rat model. *Br J Anaesth* 1985; **57**: 420–23

24 Hift RJ, Meissner PN, Meissner DM, Petersen LA. *Porphyria: A Guide for Patients and Doctors.* Cape Town: University of Cape Town, 1999

25 Hughes PJ. Propofol in acute porphyrias. *Anaesthesia* 1990; **45**: 415

26 Jackson S. Genetic and metabolic diseases. Inborn errors of metabolism. In: Katz J, Benumof J, Kadis L, eds. *Anaesthesia and Uncommon Diseases*, 3rd edn. Philadelphia: WB Saunders, 1990; 84–99

27 Jensen NF, Fiddler DS, Striepe V. Anesthetic considerations in porphyrias. *Anesth Analg* 1995; **80**: 591–9

28 Joyau M, Deybach JC, Durand M, Parmentier G, Nordmann Y. Peridural anesthesia with procaine and fentanyl in a parturient with acute intermittent porphyria. *Ann Franç Anesthes Reanimat* 1986; **5**: 453–5

29 Kantor G, Rolbin SH. Acute intermittent porphyria and caesarean delivery. *Can J Anaesth* 1992; **39**: 282–5

30 Lin YC, Chen L. Atracurium in a patient with acute intermittent porphyria. *Anesth Analg* 1990; **71**: 440–41

31 McLouglin C. Use of propofol in a patient with porphyria. *Br J Anaesth* 1989; **62**: 114

32 McNeill MJ, Bennet A. Use of regional anaesthesia in a patient with acute porphyria. *Br J Anaesth* 1990; **64**: 371–3

33 Medenica R, Lazovic G, Long P, Corbitt W, Powell D.

Plasmapheresis combined with somatostatin is a successful treatment of porphyrias. *Ther Apher* 1997; **1**: 159–64

34 Meissner PN. Enzyme studies in variegate porphyria. PhD thesis. Cape Town. University of Cape Town, 1990

35 Meissner PN, Dailey TA, Hift RJ *et al*. A R59W mutation in human protoporphyrinogen oxidase results in decreased enzyme activity and is prevalent in South Africans with variegate porphyria. *Nature Genet* 1996; **13**: 95–7

36 Meissner PN, Harrison GG, Hift RJ. Propofol as an i.v. anaesthetic induction agent in variegate porphyria. *Br J Anaesth* 1991; **66**: 60–65

37 Mitterschiffthaler G, Theiner A, Hetzel H, Fuith LC. Safe use of propofol in a patient with acute intermittent porphyria. *Br J Anaesth* 1988; **60**: 109–11

38 Moore MR, McColl KE, Rimington C, Goldberg A. *Disorders of Porphyrin Metabolism*. London: Plenum, 1987

39 Morris DL, Dudley MD, Pearson RD. Coagulopathy associated with hematin treatment for acute intermittent porphyria. *Ann Intern Med* 1981; **95**: 700–701

40 Mustajoki P, Heinonen J. General anesthesia in "inducible" porphyrias. *Anesthesiology* 1980; **53**: 15–20

41 Mustajoki P, Nordmann Y. Early administration of heme arginate for acute porphyric attacks. *Arch Int Med* 1993; **153**: 2004–8

42 Neilson IR, Singer MA, Marks GS. Association between the membrane-fluidizing properties and porphyrin-inducing activity of alfaxolone and related steroids. *Mol Pharmacol* 1980; **18**: 144–7

43 Parikh RK, Moore MR. Anaesthetics in porphyria: intravenous induction agents. *Br J Anaesth* 1975; **47**: 907

44 Parikh RK, Moore MR. Effect of certain anaesthetic agents on the activity of rat hepatic delta-aminolaevulinate synthase. *Br J Anaesth* 1978; **50**: 1099–103

45 Paslin DA. The porphyrias. *Int J Dermatol* 1992; **31**: 527–39

46 Rigg J, Petts V. Acute porphyria and propofol. *Anaesthesia* 1993; **48**: 1108

47 Rizk SF, Jacobson JH, Silvay G. Ketamine as an induction agent for acute intermittent porphyria. *Anesthesiology* 1977; **46**: 305–6

48 Roberts BA. 'Hereditary coproporphyria'. *Anaesth Intens Care* 1990; **18**: 138–9

49 Roby HP, Harrison GA. Anaesthesia for coronary artery bypass in a patient with porphyria variegata. *Anaesth Intens Care* 1982; **10**: 276–8

50 Rushman GB, Jooste CA. Anaesthesia for the porphyric patient. *Anaesthesia* 1993; **48**: 1009

51 Shipton EA, Roelofse JA. Anaesthesia in a patient with variegate porphyria undergoing coronary bypass surgery. A case report. *S Afr Med J* 1984; **65**: 53–4

52 Silvay G, Miller R, Tausk C. Safety of ketamine in patients with acute intermittent porphyria. Case reports. *Acta Anaesthesiol Scand* 1979; **23**: 329–30

53 Slavin SA, Christoforides C. Thiopental administration in acute intermittent porphyria without adverse effect. *Anesthesiology* 1976; **44**: 77–9

54 Sneyd JR, Kreimer-Birnbaum M, Lust MR, Heflin J. Use of sufentanil and atracurium anesthesia in a patient with acute porphyria undergoing coronary artery bypass surgery. *J Cardiothorac Vasc Anesth* 1995; **9**: 75–8

55 Stevens JJ, Kneeshaw JD. Mitral valve replacement in a patient with acute intermittent porphyria. *Anesth Analg* 1996; **82**: 416–18

56 Taylor RL. Magnesium sulfate for AIP seizures. *Neurology* 1981; **31**: 1371–2

57 Tenhunen R, Mustajoki P. Acute porphyria: treatment with heme. *Sem Liver Dis* 1998; **18**: 53–5

58 Tidmarsh MA, Baigent DF. Propofol in acute intermittent porphyria. *Br J Anaesth* 1992; **68**: 230

59 Weir PM, Hodkinson BP. Is propofol a safe agent in porphyria? *Anaesthesia* 1988; **43**: 1022–3