Safety of general anaesthesia and surgery in acute hepatic porphyria

S B Dover, L Plenderleith, M R Moore, K E L McColl

Abstract

Patients with acute hepatic porphyria are denied essential operations because of concern that general anaesthesia and surgery will precipitate a life threatening porphyric crisis. This study assessed the safety of surgery under general anaesthesia in these patients. A combined prospective and retrospective case note study, with a biochemical study, was conducted in 25 patients with acute hepatic porphyria undergoing 38 surgical operations. Clinical outcome measures were survival and occurrence of porphyric crisis after surgery. The biochemical activity of porphyria was assessed by measurement of the perioperative 24 hour excretion of the haem precursors δ aminolaevulinic acid (ALA) and porphobilinogen (PBG). There were no deaths or crises after 29 operations in 19 patients who were known to have porphyria before their surgery, and therefore given only appropriate drugs. These operations include such major procedures as mitral valve replacement, hip replacement, coronary artery grafting, cholecystectomies, and renal transplantation. In eight of these patients the urinary excretion of ALA and PBG were studied, and showed no sustained postoperative increase. Nine operations were performed in eight patients before the diagnosis of porphyria was known and who thus received routine anaesthetic agents. Seven of these patients developed a postoperative porphyric crisis. Two of them died. It is concluded therefore that even the most major surgery can be undertaken safely in patients with porphyria. The risk is for undiagnosed cases.

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University Department of Medicine and Therapeutics
S B Dover
M R Moore
K E L McColl

and Department of Anaesthesia, Western Infirmary, Glasgow
L Plenderleith

Correspondence to:
Dr S Dover, Department of Gastroenterology, Level 8, Gartnavel General Hospital, 1053, Great Western Road, Glasgow G12 0YN.

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The acute hepatic porphyrias are a group of inherited metabolic disorders of the haem biosynthetic pathway.¹ The cardinal feature of these diseases is the development of acute crises, which have an appreciable mortality. Episodes are characterised by severe abdominal pain, paralysis, seizures, hypertension, and tachycardia. During the porphyric episode, there is overproduction and increased urinary excretion of the haem precursors formed proximal to the metabolic block – that is, δ amino laevulinic acid (ALA) and porphobilinogen (PBG). The activity of the porphyria can be assessed by measuring their 24 hour urinary excretion.

Because the porphyrias are a group of metabolic liver diseases characterised by episodic abdominal pain, many of these patients and their families are under the care of gastroenterologists, hepatologists or surgeons. Because they are rare diseases, few such physicians have wide experience of their treatment, and therefore guidelines from specialist centres are particularly important.

Acute porphyric crises can be precipitated by a variety of factors including certain drugs, starvation, infection, and metabolic stress.² These factors come together at the time of a surgical operation. Patients with acute hepatic porphyria may thus be denied surgical treatment for coexisting diseases, because of fear of precipitating a life threatening porphyric crisis.

We have been aware of patients with porphyria undergoing major surgery without complication, of others having a crisis after minor surgery, and also of surgeons denying essential surgery to patients because of porphyria. This has prompted us to review the surgical experiences of our patients to try and identify risk factors and suggest guidelines for safe anaesthesia and surgery in acute hepatic porphyria.

Methods

This was a combined retrospective and prospective study. For the retrospective part, case records were reviewed and patients interviewed to identify previous surgical operations before or after the diagnosis of porphyria was made. Attempts were then made to obtain the hospital records including operation and anaesthetic notes and details of any postoperative problem.

For the prospective part we studied eight known porphyric patients undergoing a variety of operations. In five of these cases it was possible to assess the activity of their porphyria perioperatively by monitoring the 24 hour urinary excretion of porphyrin precursors. Urinary ALA and PBG concentrations were measured by spectrophotometric assay.³

Results

Altogether 38 surgical operations were identified among 25 patients (18 women). Thirty of these operations were performed in 20 patients with acute intermittent porphyria, seven operations in four patients with variegate porphyria, and one in a patient with hereditary coproporphyria. Eighteen operations in 11 patients were done in our own hospital, and 20 operations in 15 patients elsewhere. Nine

TABLE I Operations and their outcome in patients known to have porphyria

Patient	Sex	Porphyria	Age	Operation
1	F	VP	62	Cholecystectomy*
2	M	AIP	37	Vagotomy, cholecystectomy, and splenectomy
3	M	AIP	45	Total hip replacement*
4	F	AIP	49	Renal impairment*
4	F	VP	42	EUA+D and C
			42	Total abdominal hysterectomy
			46	Cholecystectomy*
5	F	AIP	52	Cholecystectomy*
6	F	AIP	52	Evacuation of uterus*
7	F	AIP	55	Mitral valve replacement
			64	Femoropopliteal vein graft*
8	F	AIP	48	Caesium implant*
9	F	AIP	54	Renal transplant
10	F	AIP	47	Total abdominal hysterectomy
11	M	AIP	5	Dental clearance
12	F	VP	74	Laparotomy, drainage of sub-phrenic and retroperitoneal abscess
13	F	AIP	34	Toe fusion
14	F	AIP	62	Mastectomy and axillary clearance
15	F	AIP	51	Coronary artery vein graft
16	M	AIP	46	Vagotomy and pyloroplasty
17	F	AIP	49	Insertion of Tenckhoff catheter
			49	Removal and replacement of Tenckhoff catheter
			50	Renal transplant
			52	Laparotomy and Hartman's procedure
			52	Reversal of colostomy
			53	Transplant nephrectomy
18	F	AIP	24	D and C
			26	D and C, laparoscopy and tubal ligation
25	M	HCP	49	Spinal laminectomy

AIP=acute intermittent porphyria, VP=variegate porphyria, HCP=hereditary coproporphyria, EUA=examination under anaesthesia, D and C=dilatation and curettage.
*Perioperative porphyrin biochemistry available (see Figure).

operations were performed in eight patients before the diagnosis of porphyria was made, and 29 operations in 19 known porphyric patients. There are biochemical data concerning one operation each in eight patients.

SURGERY IN PATIENTS KNOWN TO HAVE ACUTE PORPHYRIA

Twenty nine operations were performed on 19 patients known, before the time of surgery, to have acute porphyria (15 acute intermittent porphyria, 3 variegate porphyria, 1 hereditary coproporphyria). There were 14 women and five men, mean age at time of operation 46.5 years (range 5 to 74). The operations ranged from minor procedures to open heart surgery (Table I). In all of these patients anaesthetics and perioperative drugs believed to be unsafe in porphyria were avoided. Table II shows details of the anaesthetics and other drugs given to these patients.

None of the 29 operations in these 19 patients recognised as having porphyria preoperatively precipitated a clinical attack of porphyria. There were minor complications in four (an antibiotic associated rash, troublesome constipation, continuing abdominal discomfort, and a ketamine nightmare). The

only serious complication was a small stroke on the fourth day after a renal transplant. The only mechanism by which this could be attributable to porphyria would be as a feature of a hypertensive crisis, which it was not.

The Figure shows the PBG and ALA excretions in the five patients in whom it was monitored perioperatively. The five operations were hip replacement (patient 2), cholecystectomy (patients 4 and 5), evacuation of uterus (patient 6), and femoropopliteal bypass grafting (patient 7).

Only patient 2 had a significantly increased ALA excretion – more than four times the upper limit of normal preoperatively; it doubled on the third postoperative day, but had returned to preoperative values by the seventh postoperative day. The other three patients for whom preoperative values are available show no rise in ALA excretion after surgery. Patient 7, for whom there are no preoperative data (because it was an emergency operation), did show a postoperative rise, but not to values associated with a porphyric crisis.

The PBG excretion was normal in three of the patients preoperatively. In two of these it did not change postoperatively, but in the other one it increased between the second and third postoperative days, but had returned to within the normal range by day 4. In one patient the PBG value was increased preoperatively; it nearly doubled on the third and fourth postoperative days, but was back to preoperative values by day 7. The patient for whom there were no preoperative data also showed a transient rise between days 2 and 4.

None of the transient rises in ALA or PBG was associated with clinical evidence of disease activity or crisis.

Less complete biochemical data are available for three further patients. Patient 1 had normal values of ALA and PBG on the second postoperative day. In patient 3 urine analysis was not possible preoperatively as he was receiving haemodialysis. Two days after his renal transplant, however, urinary excretion of ALA and PBG were normal. Because of her radioactive implant, patient 8 could not have urine collected on the day of operation or first day afterwards, but a preoperative collection, and one on the second postoperative day were both normal. These data do not point to perioperative activation of porphyria in any of the three cases.

TABLE II Anaesthetic and other drugs used in the patients known to have porphyria

Premedication		Induction		Paralysis		Maintenance		Reversal	
Temazepam	4	Propofol	15	Suxamethonium	10	Nitrous oxide	18	Neostigmine	4
Cyclizine	4	'Inhalation'	3	D-turbocurapine	8	Propofol infusion	8	Atropine	3
Atropine	4	Halothane	2	Atracurium	5	Morphine	5		
Morphine	3	Ketamine	2	Neostigmine	4	Ethrane	3		
Lorazepam	2	Nitrous oxide	1	Vancuronium	1	Isoflurane	6		
Chlorpromazine	2	Etomidate	2			Pentazocine	2		
Myoscine	1	Fentanyl	2			Fentanyl	4		
Omnopon	1	Diazemuls	1			Alfentanyl	1		
Fentanyl	1	Alfentanyl	1			Pethidine	1		
Droperidone	1	Midazolam	1			Halothane	1		
						Ether	1		
						Ketamine	1		
						Diazemuls	1		

TABLE III Operations and their outcome in patients with undiagnosed porphyria

Patient	Sex	Porphyria	Age	Operation	Outcome
4	F	VP	21	Appendicectomy*	Post operation crisis. Abdominal pain and paralysis. Diagnosed and survived. Persisting paraparesis
9	F	AIP	33	Ovarian cystectomy*	Crisis after operation. Worsening of pain and severe hypertension. Recovered
19	F	AIP	32	Removal of transitional cell papilloma on nose and plastic reconstruction	Post operation crisis. Abdominal pain, hyponatraemia seizures. Diagnosed. Recovered
20	F	VP	52	Emergency cholecystectomy*	Died of porphyric crisis despite diagnosis and haem therapy
21	M	AIP	40	Investigative laparotomy*	Developed paralysis and pain. Died day 4. Undiagnosed until grand-daughter developed disease
22	F	AIP	19	Laparotomy and hysteropexy Abdominal hysterectomy*	Uncomplicated recovery
23	F	AIP	7	Appendicectomy*	Uncomplicated recovery. Diagnosis made when daughter developed disease
24	F	AIP	19	Appendicectomy*	Post operative worsening of pain. Seizures. Crisis diagnosed. Anti-convulsants withdrawn. Survived
					Post operative psychosis, progressed to seizures and paralysis before diagnosis. Incomplete recovery. Appendix normal

*Operation (probably) performed for symptoms of unrecognised porphyric attack. Abbreviations as in Table I.

OPERATIONS UNDERTAKEN BEFORE THE DIAGNOSIS OF PORPHYRIA WAS KNOWN We have identified nine operations that were performed in eight patients (seven women), before the diagnosis of porphyria was recognised (Table III). Six patients had acute intermittent porphyria, and two variegate porphyria, with a mean age at time of operation of 30 years (range 7–52). There were only two uncomplicated recoveries with seven crises resulting in two deaths.

Abdominal pain, usually similar to that for which the operation had been performed, was a feature in all seven postoperative crises. Three patients had seizures, one associated with a serum sodium of 112 mmol/l resulting from the syndrome of inappropriate antidiuretic hormone secretion. Four had considerable neuropathy, one hypertension, and one a psychosis.

Discussion

This study shows that surgery can be undertaken safely in patients with acute porphyria, provided that contraindicated drugs and anaesthetic agents are avoided. It also emphasises the danger of surgery in patients not recognised to have porphyria and who therefore receive contraindicated drugs.

None of the 29 operations performed in patients known to have porphyria resulted in clinical consequences attributable to porphyria. In addition, eight patients already known to have porphyria showed no evidence

of a sustained rise in markers of disease activity over preoperative values. The transient rises in ALA or PBG that were seen in three patients were not associated with clinical evidence of disease activity. They may represent sub-clinical disease activity, associated with some aspect of the operation, for example, drugs, starvation, stress, etc.⁴ Alternatively these rises may not truly be reflecting disease activity, perhaps resulting from increased haem synthesis due to blood loss, or a consequence of blood transfusion.⁵

This study also confirms that provided the necessary precautions are taken patients with porphyria can safely undergo even the most major surgery, for example heart valve replacement, coronary artery grafting, and hip replacement.^{6 7}

Propofol was the most commonly used intravenous anaesthetic agent, confirming a previous prospective study of its safety in variegate porphyria.⁸ There is, however, a report of biochemical activation of porphyria after propofol administration.⁹ The choice of drugs and anaesthetics used in the patients known to have porphyria was based on clinical experience^{10–12} and animal studies.¹³ This type of information has been compiled for clinical use,¹⁴ and its value is supported by the favourable outcome of the patients in this study.

In addition to the correct choice of anaesthetic and drugs, it is important to avoid starvation¹⁵ in the perioperative period, as this can also trigger an attack; patients should be given intravenous glucose¹⁶ perioperatively, until able to resume an adequate diet. Because of the danger of hyponatraemia in acute porphyria (caused by the syndrome of inappropriate secretion of antidiuretic hormone – see patient 19’s first operation) the serum sodium should be monitored.

In contrast with the favourable outcome in the patients known to have an acute porphyria at the time of surgery, the outcome in those in whom the diagnosis was not known was extremely poor with seven crises resulting in two deaths, and only two uncomplicated recoveries. The information about the operations performed, and the anaesthetic agents used in these patients is much less complete because at the time they were of no particular

(A) Perioperative 24 hour urinary excretion of δ aminolaevulinic acid (ALA); (B) perioperative 24 hour urinary excretion of porphobilinogen (PBG).

interest, and in some cases records have been destroyed or become unavailable. It can be assumed, however, that these patients received standard anaesthetics, most of which are highly porphyrinogenic.^{13 14} This probably explains the poor outcome.

Moreover, in retrospect, it seems probable that seven of these nine operations were undertaken for symptoms of porphyria. These operations, where the diagnosis was unknown and the disease was active, were particularly hazardous; with two fatal and two non-fatal crises, and only one patient recovering without complication, twice. This is similar to previous reported experience,¹⁷ where all seven patients given thiopental to induce anaesthesia during an acute symptomatic episode of porphyria worsened biochemically and clinically.

Because acute porphyria is an uncommon disease, which can mimic other conditions, it is likely to have caused other undiagnosed postoperative deaths and morbidity. Patients with porphyria need appropriate treatment when they develop a true abdominal surgical emergency, though this can be difficult to diagnose.¹⁸

Three patients had operations before the diagnosis was made, and further surgery afterwards. The prediagnosis operations were minor (two appendicectomies and one ovarian cystectomy) compared with the postdiagnosis operations (total hysterectomy, cholecystectomy, and renal transplant). Nevertheless, these patients each had a porphyric crisis as a result of the anaesthetic and minor operation undertaken before diagnosis, but had no complications of porphyria after operations when they were known to be porphyric, and thus received only safe agents.

The problem of patients being denied surgery because of porphyria is exemplified by patient 14. Her original surgeon and his anaesthetist would not undertake lumpectomy for a small breast tumour. She could not be given endocrine treatment because of its porphyrinogenicity.¹⁴ Eighteen months later she re-presented with extensive local disease requiring mastectomy and axillary clearance for cosmesis and local control. She later died of

metastatic disease. This outcome may have been avoided by earlier and less mutilating surgery.

In conclusion, this study shows that even major and repeated surgery can be performed without complication in patients with acute hepatic porphyria. Safety depends upon a knowledge of the diagnosis and which anaesthetic agents are safe. The risk is for undiagnosed cases, and continued awareness of the features of this disease is required to prevent crises and deaths.

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