J Anesth (1999) 13:115–118

Journal of Anesthesia

Anesthetic management for a patient with acute intermittent porphyria treated with heme arginate

Sumio Amagasa[1], Mayumi Yamakawa[1], Ritsuko Fukuda[1], Seiji Takaoka[1], Hisao Tanaka[1], Hideo Horikawa[1], and Hikaru Hoshi[2]

[1] Department of Anesthesia and Resuscitation, Yamagata University School of Medicine, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan
[2] Intensive Care Unit, Yamagata University Hospital, 2-2-2 Iida-Nishi, Yamagata 990-9585, Japan

Key words: Acute intermittent porphyria, Heme arginate, Propofol

Introduction

Acute intermittent porphyria (AIP) is the major autosomal dominant acute hepatic porphyria and is characterized by an approximately 50% deficiency of porphobilinogen (PBG) deaminase activity. This deficiency leads to a decrease in the pool of free heme and to excessive activity of the heme precursors δ-aminolevulinic acid (ALA) and PBG by markedly stimulating ALA synthase [1]. In Europe, heme arginate (Normosang, Medica Pharmaceutical, Helsinki, Finland) has been the most reliable in normalizing excess ALA and PBG excretion by ALA synthase inhibition via a negative feedback mechanism derived from the supplement of liver heme (Fig. 1) [2,3]. However, safety criteria for the use of anesthesia-related drugs in porphyric patients have not been fully established. In the present report, we describe a case of successful anesthetic management of AIP using propofol and fentanyl in combination with heme arginate treatment.

Case report

A 29-year-old woman (height, 152 cm; weight, 40 kg) was scheduled for ethmoidectomy and sphenoidectomy for an abscess in the paranasal sinus. In April 1996, the patient had undergone an emergency operation for acute severe abdominal pain, which occurred after alcoholic intake in the perimenstrual period. The cause of the abdominal pain was not found, and the details of the anesthetic management were not clear. In June 1996, the abdominal pain reccurred. Hyponatremia (119 mmol·l^{-1}) and a marked increase in urinary ALA and PBG levels to 9.3 mg·l^{-1} (normal $<$ 4 mg·l^{-1}) and 16.2 mg·l^{-1} (normal $<$ 2 mg·l^{-1}), respectively, were detected. AIP was diagnosed, and the patient was immediately treated with chlorpromazine 25 mg·day^{-1} and glucose infusion. Thereafter, the abdominal pain, which was effectively overcome by these treatments, always recurred in the premenstrual period. However, the hyponatremia accelerated to 94 mmol·l^{-1} and was treated with 10% sodium chloride infusion to approximately 120 mmol·l^{-1}. After September 27 1996, left lower abdominal pain was accompanied by generalized convulsions and sudden respiratory arrest, followed by disturbance of consciousness lasting for 15 days. The patient was transferred to our hospital on October 11, 1996.

On admission, the patient's impaired consciousness was assessed as Glasgow coma scale (GCS) 3 ~ 10; she opened her eyes but did not respond to verbal commands. She also responded to painful stimulation but not to verbal commands. She developed upper-extremity dominant flaccidity tetraplegia, bulbar paralysis, dysarthria, and dysphagia, and her posture showed signs of decorticate rigidity, with extended neck and flexing upper extremities as in opisthotonus. She frequently had localized convulsions in her eyelids and upper extremities accompanied by leftward conjugated deviation and tachycardia rising to 160·min^{-1}. Serum electrolyte analysis revealed mild hyponatremia of 124 mmol·l^{-1}. The MRI examination showed sinusitis, central pontine myelinolysis, and cortical laminar necrosis in the lateral and temporal regions. The patient was treated with antibiotics and chlorpromazine 25 ~ 75 mg·day^{-1}, cimetizine 800 mg·day^{-1}, and hyperalimentation. She was also treated with diazepam 2 mg·day^{-1} for convulsions, 10% sodium chloride for

Address correspondence to: S. Amagasa
Received for publication on April 30, 1998; accepted on November 17, 1998

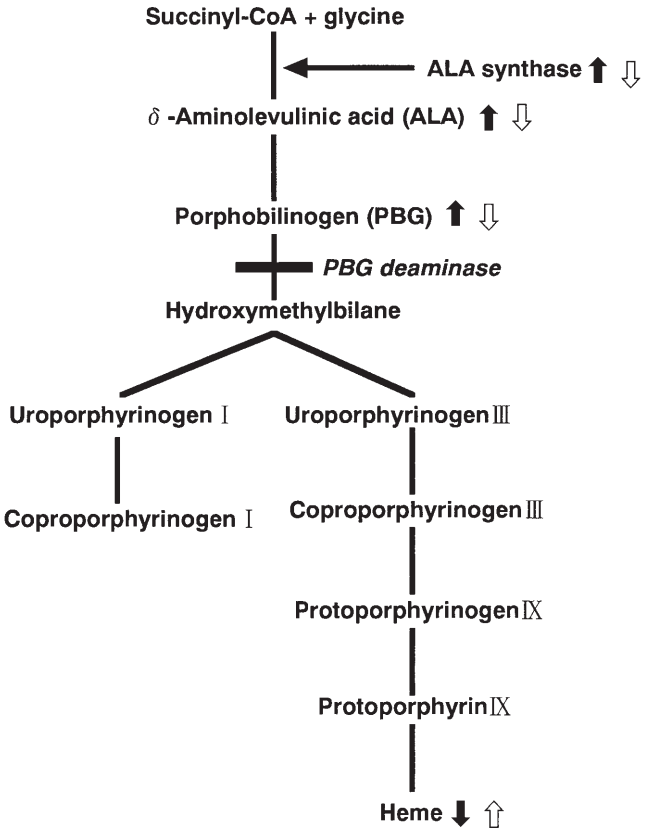

Fig. 1. Schema of the heme biosynthetic pathway modified from Kappas et al. [1] and Böhrer et al. [8]. In approximately 10% of AIP patients who have a PBG deaminase deficiency, clinical symptoms occur with exposure to situations or drugs that induce ALA synthase and hepatic cytochrome P-450 (⬆, ⬇). Heme arginate administration is effective in reducing porphyrin precursor excretion and in limiting the duration of acute attacks (⇧, ⇩)

hyponatremia, and propranolol 0.2 ~ 0.5 mg·h^{-1} for tachycardia. Although the convulsions disappeared and her heart rate was reduced to 100–120 · min^{-1} with sinus rhythm, these conservative treatments did not produce satisfactory results. The patient's urinary ALA and PBG levels increased to 20.7 mg·l^{-1} and 40.1 mg·l^{-1}, respectively, and hyponatremia accelerated to 116 mmol·l^{-1}. Consciousness disturbance and tetraplegia still did not improve. Heme arginate 100 mg·day^{-1} was introduced for 4 days starting on November 7, with a total dose of 400 mg, resulting in a marked decrease to nearby normal urinary ALA levels of 0.9 mg·l^{-1} and PBG levels of 2.8 mg·l^{-1} on November 11. Although these levels began to gradually increase again within a few days, the patient's serum sodium level improved more than 130 mmol·l^{-1} and remained at the same level. The paraplegia gradually improved except in the upper extremities. Although the patient still exhibited infantility and little or no control of her emotions, she was able to utter the sounds "ah" or "uh," could accept simple orders, and could express simple intentions. However, MRI and CT examination revealed that her sinusitis, including the formation of an abscess, had expanded widely from the right posterior ethmoidal sinus into the sphenoidal and maxillary sinuses. These findings suggested the possibility that these large infectious areas might spread through the intracranial cavity and interfere with the improvement in clinical AIP symptoms. Consequently, ethmoidectomy and sphenoidectomy were scheduled. Prednisolone 5–10 mg·day^{-1} was additionally administered 7 days before surgery to facilitate the penetration of antibiotics into the infectious areas by diminishing their surrounding tissue edema.

The conservative treatments of chlorpromazine 50 mg·day^{-1}, cimetizine 800 mg· day^{-1}, propranolol 0.2 mg·h^{-1}, and hyperalimentation were continued. However, urinary ALA and PBG levels had already increased to 21.2 mg·l^{-1} and 46.8 mg·l^{-1}, respectively, on December 2. Since urinary ALA and PBG levels increased gradually, heme arginate 100 mg·day^{-1} was administered again for 2 days, on the day before surgery (December 9) and just before surgery on December 10, with a total dose of 200 mg, to rapidly reduce ALA and PBG levels, avoiding acute perioperative exacerbation. Chlorpromazine 50 mg in normal saline 100 ml was infused on the morning of the operation. The patient was premedicated intramuscularly with 20 mg of famotidine. On arrival in the operating theater, her heart rate was 122 · min^{-1} with sinus rhythm and her blood pressure was 136/68 mmHg. After placement of the left radial artery cannula, anesthesia was gradually and carefully induced using intravenous bolus administrations of propofol 80 mg and fentanyl 100 μg. These were followed by vecuronium 4 mg; the patient was then easily intubated, and propranolol infusion was discontinued. Anesthesia was maintained with continuous infusion of propofol 5 ~ 7 mg·kg^{-1}·h^{-1} and fentanyl 100 μg, under oxygen and air. No marked changes in blood pressure, blood gases, or serum electrolytes were observed during surgery. The patient was extubated shortly after the surgery when she had sufficiently awakened from the anesthesia. She was then immediately transferred to the ICU ward because of an unwanted porphyric attack that could have been caused by the stress of surgery. Treatments with chlorpromazine, cimetizine, hyperalimentation, and prednisolone was restarted. No rise in the level of heme precursors in the patient's urine obtained during anesthesia was detected by means of optical density scanning. ALA and PBG levels on the first postoperative day remained low: 1.1 mg·l^{-1} and 6.8 mg·l^{-1}, respectively. The patient did not complain of unbearable pain. On the following day, because the patient's temperature rose above 38°C, an acetaminophen suppository was used once. Administration of heme arginate 100 mg was initiated. The patient was

transferred to an otorhinolaryngological ward without any systemic deterioration. ALA and PBG levels on the second postoperative day were 0.9 mg·l^{-1} and 3.5 mg·l^{-1}, respectively. On the third postoperative day, heme arginate 100 mg was administered again. Convulsions were not observed postoperatively, and the patient's neurological symptoms gradually improved so that she could sit on the bed and operate a TV remote control by herself. After the patient became alert and cooperative and was assessed as GCS 1, she was transferred to another hospital on January 11, 1997. Thereafter, although the patient's dysarthria remained, she recovered to the point of being able to drive a car independently.

Discussion

Clinical AIP symptoms usually occur with exposure to precipitating situations that increase the demand for heme biosynthesis, such as menstruation, pregnancy, infections, inadequate nutrition, overwork, surgery, excessive alcoholic intake, and the administration of drugs such as barbiturates that induce hepatic microsomal cytochrome P-450. These processes are potentially accompanied by excess production and excretion of ALA and PBG, and also may intermittently induce acute exacerbation (Fig. 1) [1]. Our patient might have triggered AIP by excessive alcoholic intake in her perimenstrual period. Thereafter, her clinical condition quickly deteriorated, and it was not possible to overcome these symptoms by conventional therapeutic means. The patient's central pontine myelinolysis and cortical laminar necrosis might have been caused by the AIP-induced rapid change in serum sodium levels, or perhaps was related to a cerebral vasospasm. However, the details are still unknown. Heme arginate was imported immediately from Finland. After obtaining special permission from the patient's family and from the Ministry of Health and Welfare of Japan, and the approval of our institutional ethics committee, heme arginate was deliberately administered to improve the consciousness disturbance by restoring hyponatremia and eliminating porphyrins and porphyrin precursors, which might have had a bad influence on the patient's consciousness. A 100-mg dose of heme arginate, which is stable for several years [3], was diluted in 100 ml of physiologic saline and infused via the subclavian vein over 2 h while being shielded from light. Since heme arginate itself could be associated with coagulopathy or thrombophlebitis [1], its use is generally limited to only a few days if the patient's clinical condition becomes much worse. However, since approximately 1 week was needed to determine the effect on urinary ALA and PBG levels, heme arginate was administered for 4 days during the perioperative period to prevent acute exacerbation, resulting in a marked decrease in ALA and PBG levels. The patient's blood coagulation activity was checked periodically during her hospitalization. Prothrombin time (PT) and activated partial thromboplastin time (APTT) remained within standard values. Both fibrinogen and fibrin degradation product (FDP) slightly exceeded standard values temporarily. Fortunately, no significant changes in these values were observed after the administration of heme arginate. Heme arginate should therefore be used routinely in Japan, even in severe cases of AIP accompanied by tetraplegia, bulbar paralysis, and disturbance of consciousness.

Administration of a lipophilic drug such as propofol, which induces hepatic ALA synthase or activates the cytochrome P-450 system in the liver, may also contribute to a porphyric crisis [1]. Therefore, many drugs commonly used in clinical anesthesia have already been classified as safe, unsafe, on contentious for use in porphyric patients (Table 1). However, these classifications have been made only on the basis of practical outcome or the results of animal studies. We should choose appropriately safe drugs for anesthetic management in porphyric patients. Weir and Hodkinson [6] have advised against the use of propofol because of marked increases in porphobilinogen, uroporphyrin, and coproporphyrin following its use in a patient with variegata porphyria. Propofol, together with fentanyl, was recently classified as a safe drug. Shaw et al. [7] have reported an uneventful and successful course of electroconvulsive therapy using propofol in an AIP patient. Böhrer et al. [8] have shown that propofol does not exert any significant porphyrinogenic effects in experimental rat models. In the present case, a marked decrease in ALA and PBG levels was obtained in response to heme arginate pretreatment, and propofol and fentanyl caused no systemic and neurological deterioration during and after anesthesia, indicating that the combination of these drugs does not increase heme precursor activity. Therefore, we recommend propofol and fentanyl anesthesia in combination with heme arginate perioperative treatment in AIP patients.

In summary, in an AIP patient with severe clinical symptoms, total intravenous anesthesia using propofol and fentanyl in combination with heme arginate treatment is a simple and effective method that results in a decrease in ALA and PBG levels, although at present heme arginate is not available for clinical use in Japan.

Acknowledgments. The authors wish to thank Professor Emeritus Hideo Sasaki and Shinji Susa, M.D. (Third Department of Internal Medicine), for their valuable advice. This report was presented in part at the 17th Annual Meeting of the Japan Society for Clinical Anesthesia in Kokura in 1997.

Table 1. Safety of anesthesia—related drugs in porphyric patients

Safe–possibly safe	Unsafe–probably unsafe	Contentious (C) or no data (N)
Propofol	Barbiturates[a,b,c]	Ketamine (C)[a,b]
Midazolam	Flunitrazepam[a,b]	Diazepam (C)[a]
Droperidol	Etomidate[a,b]	
Nitrous oxide	Enflurane[b]	Halothane (C)[a,b]
		Isoflurane (N)
Suxamethonium		Pancuronium (C)[b]
Vecuronium		
Atropine		
Neostigmine		
Morphine	Pentazocine[a,b,c]	Alfentanil (N)
Fentanyl[b]		Sufentanil (N)
Buprenorphine		
Naloxone		
Procaine[b]	Mepivacaine[b]	Lidocaine (C)[a,b]
		Bupivacaine (C)[b]
Adrenaline		α-Agonist (N)
Procainamide		β-Agonist (N)
β-Blocker	Verapamil	Sodium nitroprusside (N)
	Nifedipine[b]	Mexiletine (N)
	Diltiazem	Disopyramide (C)
		Ranitidine (C)
Cimetidine	Endogenous steroids[a,b,c]	
Corticosteroids	Theophylline[a]	
Salbutamol	Carbamazepine[b,d]	

Modified from Kappas et al. [1], Harrison et al. [4], and Jensen et al. [5].
[a] Clinical report on porphyric crisis or acute attacks.
[b] Porphyrinogenic in animal experiments or cell cultures.
[c] Triggers porphyric crisis by selectively increasing the synthesis of ALA synthase.
[d] Directly inhibits heme synthesis.

References

1. Kappas A, Sassa S, Galbraith RA, Nordmann Y (1995) The porphyrias. In: Scriver CR, Beaudet AC, Sly WS, Valle D (eds) The metabolic and molecular bases of inherited disease, 7th edn. McGraw-Hill, New York, pp 2103–2159
2. Mustajoki P, Nordmann Y (1993) Early administration of heme arginate for acute porphyric attack. Arch Intern Med 153:2004–2008
3. Tenhunen R, Tokola O, Lindén B (1987) Haem arginate: a new stable haem compound. J Pharm Pharmacol 39:780–786
4. Harrison GG, Meissner PN, Hift RJ (1993) Anaesthesia for the porphyric patient. Anaesthesia 48:417–421
5. Jensen NF, Fiddler DS, Striepe V (1995) Anesthetic considerations in porphyrias. Anesth Analg 80:591–599
6. Weir PM, Hodkinson BP (1988) Is propofol a safe agent in porphyria? Anaesthesia 43:1022–1023
7. Shaw IH, McKeith IG (1998) Propofol and electroconvulsive therapy in a patient at risk from acute intermittent porphyria. Br J Anaesth 80:260–262
8. Böhrer H, Schmidt H, Martin E, Lux R, Bolsen K, Goerz G (1995) Testing the porphyrinogenicity of propofol in a primed rat model. Br J Anaesth 75:334–338