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Anesthetic management for congenital erythropoietic porphyria: report of a case

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Introduction

Porphyrias are a group of inborn metabolic derangements caused by defects in specific enzyme activities in heme biosynthesis. There are seven porphyrias according to the major site of the affected enzyme. Their clinical features are mainly classified into three types: neuroporphyria, cutaneous porphyria, and the combined type [1]. An awareness of porphyrias is essential to any anesthetist, but cutaneous porphyria, characterized by photosensitivity of the skin, has not been sufficiently stressed in the anesthetic literature. This is in contrast to the concerns over acute porphyric crises of neuroporphyria related to life-threatening neurologic disorders, which can be precipitated by some drugs in common use in anesthetic practice [2,3]. Serious complications have been encountered that can be attributed to photosensitivity in cutaneous porphyria, with resultant phototoxic burn of the skin and intraabdominal organs exposed to lights in the operating room [4,5]. Congenital erythropoietic porphyria (CEP) is a rare form of cutaneous porphyrias that is always associated with severe light-induced injury [6]. There have been several reports about anesthetic management for neuroporphyrias [1–3], whereas little or no information about cutaneous porphyrias is available. This report describes anesthetic considerations for a patient with CEP presenting for skin transplantation.

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Case report

The patient was a 29-year-old, 81-kg man with no family history of porphyria. He was admitted with a refractory ulcer on his right hand. He was noted at birth to have hepatomegaly and hyperbilirubinemia. A diagnosis of CEP was confirmed on the basis of increased urinary uroporphyrin in early childhood. He had been suffering from marked photosensitivity of the skin, leading to blisters on his hands, nose, and cheeks. The patient sustained a small ulcer on the back of his right hand after trivial trauma 2 years ago. The skin lesion did not improve under medical treatment with antiseptics and antibiotics, culminating in an intractable triangular-shaped ulcer with a 5-cm base. He was scheduled for skin transplantation, the first operation in his life. The coexistence of diabetes mellitus was recognized 3 years before, and he has taken oral hypoglycemic agents. Preoperative laboratory data were normal except for mild increases in total bilirubin 1.5 $mg \cdot dl^{-1}$, reticulocyte 26%, LDH 717 $IU \cdot l^{-1}$, total cholesterol 278 $mg \cdot dl^{-1}$, and blood glucose 194 $mg \cdot dl^{-1}$. On physical examination his cheeks had developed a phototoxic skin reaction with porphyrin deposition of dark brown pigmentation. The patient was so obese that he was suspected to have difficulty in maintaining the airway under general anesthesia. In these circumstances the laryngeal mask airway (LMA) has gained popularity as a valuable alternative for airway management, especially in the spontaneously breathing patient. Therefore we postulated that an LMA would be more appropriate for his anesthetic care once it was properly in place.

After placement of the standard monitors, anesthesia was induced with intravenous ketamine 80 mg and midazolam 2 mg. A size 4 LMA was inserted and attached firmly by the endotracheal tube holder (Hudson RCI, Temecula, CA, USA). Then the holder was secured around the back of the patient's neck with a cloth tie and not with a sticking plaster. Correct positioning of

the LMA was performed with a bronchofiberscope. Immediately before skin incision, propofol 200 mg was given and anesthesia was maintained with inhaled 66% nitrous oxide in oxygen, 0.7%–1.5% halothane, and continuous intravenous ketamine ($1.2\,mg \cdot kg^{-1} \cdot h^{-1}$), with no muscle relaxant. Spontaneous breathing was allowed to return, assisted with bag ventilation as necessary, transiently leading to slight hypercapnia with a maximal $PaCO_2$ of 51.5 mmHg. Control of blood glucose levels required intravenous insulin at 1 to 2 units per hour. No measures were taken to protect the patient from operating lights. Only a small amount of blood loss was estimated during the operation, which lasted for 104 min. Intraoperative fluid replacement consisted of 600 ml acetate Ringer's solution containing 4% glucose. After the operation the patient was asleep on arrival in the ICU, and the LMA was extubated an hour later when he was fully alert. On the first postoperative day, urinary uroporphyrin and coproporphyrin levels were markedly elevated at $12\,200\,\mu g \cdot day^{-1}$ (normal range, $<20\,\mu g \cdot day^{-1}$) and $2854\,\mu g \cdot l^{-1}$ ($<100\,\mu g \cdot l^{-1}$), respectively, while δ-aminolevulinic acid (ALA) and porphobilinogen were within normal limits. The patient had an uneventful perioperative course and was discharged on the 24th postoperative day.

Discussion

CEP is a very rare autosomal recessive disease. There have been only 40 case reports in Japan to date [6]. Death usually occurs in early childhood. The most common clinical symptoms and signs include severe cutaneous photosensitivity with mutilating skin lesions, facial hirsutism, hemolytic anemia, port-wine-colored urine, and osteochondrodysplasia of the nose, auricle, and fingers, some of which exist at birth. CEP causes excessive accumulation and excretion of isomer I porphyrins secondary to reduced activity of uroporphyrinogen III synthase in the bone marrow. In this case most of the urinary porphyrin was uroporphyrin and most of the fecal porphyrin was coproporphyrin, which are characteristic of CEP. The porphyrins accumulated in skin tissue are excited predominantly by ultraviolet (UV) light at a wavelength of about 400 nm, thereby emitting their corresponding fluorescent chemicals in the phototoxic reaction. Exposure of the skin to sunlight forms subepidermal bullae, erythema, and subsequent scars, probably because absorption of UV light in the presence of oxygen influences porphyrins and hydrolytic enzymes stored in the lysosomes [1]. The brightness in the operating room is generally provided by ceiling-mounted fluorescent lamps radiating an amount of power within the UV and blue part of the spectrum. Thus, shielding the patient from operating lights sounds efficacious, but with topical screens all tissues cannot be covered totally. Filtering of the light proved beneficial in terms of both its practicality and its effectiveness in the prevention of light-induced damage [7]. We should have made use of an acrylate yellow filter, if it was available in our case, although no exacerbation of the skin lesions developed without any defensive measures. For CEP patients with terribly fragile skin, special caution must be taken during positioning and transportation. It is also important to avoid the use of sticking plaster and excessive pressure on the skin from a face mask. Securing of the LMA with a cloth tie appears to be free from harm.

The choice of anesthetic agents for CEP is an inevitable consideration in preventing aggravation of the disease. ALA synthase (ALAS) is the rate-limiting enzyme for heme biosynthesis. In the liver, ALAS is regulated in a negative feedback fashion by heme, the end product of the pathway. Indeed, hepatic ALAS can be induced by barbiturates that increase the synthesis of microsomal cytochrome P-450. The porphyrinogenic activity of drugs has usually been assessed in an animal model by examining their effects on ALAS activity and the level of porphyrin intermediates, although final proof of their safety should come from clinical observations. Halothane, a widely used volatile anesthetic, has been accepted as a reliable agent for porphyrias. In this case, however, it seemed unlikely that intraoperative spontaneous breathing could be maintained safely at higher concentrations of halothane. This is why a low dose of ketamine was supplemented (for a total dose of $2.6\,mg \cdot kg^{-1}$). In addition, ketamine produces profound analgesia, and therefore a minimal requirement for analgesics can be expected after surgery. Ketamine undergoes biotransformation in the liver by the microsomal enzyme system, and conflicting reports exist as to its porphyrinogenic potential. Even so, ketamine is considered clinically safe for porphyrias in the latest hardcover [1], as with propofol or midazolam, on the basis of human experience with no apparently unfavorable effect. Now it has been verified that two isozymes are present for ALAS, one coding the erythroid form (ALAS-E) and the other coding the hepatic or nonspecific form (ALAS-N) [8]. According to recent data, the ratio of ALAS-E mRNA content to that of ALAS-N mRNA rises from roughly 10:1 in ordinary cells to 1000:1 in fully differentiated cells. Moreover, in erythroid cells both the enzymes are expressed and regulated in a distinctive manner. A potent inhibitor of heme synthesis enhanced ALAS-N activity, whereas it had no effect on ALAS-E [9], indicating that CEP is incompatible with such a drug-inducible disease as acute intermittent porphyria. Given the large number of drugs and the diversity of potentially porphyrinogenic agents, ALAS-N in erythroid cells, even in only a trace quantity, may

further facilitate porphyrin production since it is under heme-mediated feedback control, as in the liver. As few drugs as possible should be administered until confirmation has been obtained that any drug can be safely used in patients with CEP.

In summary, this report may be the first to describe the consideration of anesthetics for a patient with CEP. It is suggested that general anesthesia poses no additional risk in the affected patient, provided that special perioperative precautions are taken to circumvent exaggeration of the cutaneous lesions, while the choice of anesthetic techniques and agents remains to be made.

References

1. Orkin FK (1996) Exacerbation of inducible porphyria. In: Gravenstein N, Kirby RR (eds) Complications in anesthesiology, 2nd edn. Lippincott-Raven, Philadelphia, pp 639–651
2. Harrison GG, Meissner PN, Hift RJ (1993) Anaesthesia for the porphyric patient. Anaesthesia 48:417–421
3. Dover SB, Plenderleith L, Moore MR, McColl KEL (1994) Safety of general anaesthesia and surgery in acute hepatic porphyria. Gut 35:1112–1115
4. Bloomer JR, Weimer MK, Bossenmaier IC, Snover DC, Payne WD, Ascher NL (1989) Liver transplantation in a patient with protoporphyria. Gastroenterology 97:188–194
5. Herbert A, Corbin D, Williams A, Thompson D, Buckels J, Elias E (1991) Erythropoietic protoporphyria: unusual skin and neurological problems after liver transplantation. Gastroenterology 100:1753–1757
6. Tanigawa K, Takamura N, Yamashita S (1995) Congenital erythropoietic porphyria (in Japanese). Nihon Rinshou 53:1422–1426
7. Meerman L, Verwer R, Slooff MJH, Hattum JV, Beukeveld GJJ, Kleibeuker JH, Haagsma EB (1994) Perioperative measures during liver transplantation for erythropoietic protoporphyria. Transplantation 57:155–158
8. Riddle RD, Yamamoto M, Engel JD (1989) Expression of δ-aminolevulinate synthase in avian cells: separate genes encode erythroid-specific and non-specific isozymes. Proc Natl Acad Sci USA 86:792–796
9. Fujita H, Yamamoto M, Yamagami T, Hayashi N, Sassa S (1991) Erythroleukemia differentiation: distinctive responses of the erythroid-specific and the nonspecific δ-aminolevulinate synthase mRNA. J Biol Chem 266:17494–17502