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Safety of isoflurane and epidural anesthesia in a patient with hereditary coproporphyria

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Introduction

Porphyrias are inherited or acquired disturbances in heme synthesis, and are usually divided into two main groups, erythropoietic and hepatic, according to the two major sites of heme synthesis [1]. Among hepatic porphyrias, acute intermittent porphyria (AIP), variegate porphyria (VP), and hereditary coproporphyria (HCP) may give rise to an acute attack which presents with mild to severe abdominal and neuropsychiatric symptoms in response to stress, infection, fasting/dehydration, endogenous hormonal fluctuations, excessive alcohol intake, and certain drugs [2–4]. HCP is an autosomal dominant hepatic porphyria resulting in a deficiency of the coproporphyrinogen oxidase enzyme. The incidence of HPC is uncertain, since most patients are asymptomatic. Acute attacks are indistinguishable from those in AIP and VP and are precipitated by the same factors. During acute attacks, increased urinary excretion of δ-aminolevulinic acid (ALA) and porphobilinogen (PBG) occurs in all groups, but the patterns of porphyrins in urine and feces differ. Increased fecal excretion of coproporphyrinogen III is characteristic [2]. In the anesthetic management of such patients with porphyria, the selection of appropriate anesthetic agents and techniques is important. Although a variety of drugs have been implicated in precipitating an acute attack [5], it is difficult to predict which drugs will be porphyrogenic. There have been several reports about the anesthetic management of patients with AIP [4,6,7], but the number of case reports about HCP is small [8,9]. We report the anesthetic management of a patient with HCP. This case report describes the uneventful use of isoflurane for maintenance of anesthesia and epidural anesthesia for intra- and post-operative analgesia.

Case report

A 64-year-old man was scheduled for subtotal gastrectomy for gastric cancer. His mother and sister had both died of unknown causes during pregnancy, and his two daughters had also died of unknown causes soon after birth. He was diagnosed as having porphyria when his son died of an attack of AIP. He had no history relevant to porphyria and had received no medication. He did not have any previous anesthetic or surgical history. The results of preoperative physical examination were normal, and those of biochemical studies were unremarkable, except for blood urea nitrogen (BUN) of 32 mg·dl^{-1}. The urinary coproporphyrin I level was normal, while the coproporphyrin III level was 141.5 μg·l^{-1} (normal range: 51.0 ± 23.0 μg·$^{-1}$). The fecal coproporphyrin III level was 5000 μg per day (normal < 640 μg per day), and the protoporphyrin III level 6000 μg/day (normal < 1830 μg per day). Although he did not show any signs and symptoms of this disease, he was diagnosed with HCP due to elevated fecal and urinary coproporphyrin III levels, an elevated fecal protoporphyrin III level, and his family history.

He was premedicated with 0.5 mg of atropine sulfate. An epidural catheter was placed at the eighth thoracic intervertebral space. General anesthesia was induced with 200 μg of fentanyl and 7.5 mg of droperidol administered intravenously and nitrous oxide and isoflurane in oxygen. Following administration of 8 mg of vecuronium, tracheal intubation was performed.

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Table 1. Perioperative urinary levels of porphyrins and precursors

	Normal range	Day of operation					
		Before	During	After	2POD	6POD	9POD
Aminolevulinic acid	5 mg·l^{-1}>		2.2	5	1.4	4.2	
Porphobilinogen	1.4 mg·l^{-1}>		1	0.6	0.6	1.4	1.4
Uroporphyrin	30 μg·l^{-1}>	1>	7	8	1>	83	43
Coproporphyrin	100 μ·l^{-1}>	170	92	555	38	682	382

POD, postoperative day.

General anesthesia was maintained with inhaled 60% N_2O/40% O_2, 0.5%–1.0% isoflurane and intermittent intravenous administration of fentanyl and vecuronium. The total dose of fentanyl and vecuronium was 500 μg and 18 mg, respectively. After 5 ml bolus administration of 0.25% bupivacaine to the epidural space, a continuous epidural infusion of 0.25% bupivacaine was given during surgery at a rate of 4 ml·h^{-1}. To prevent any tendency to hypoglycemia, which may precipitate an acute attack, 500 ml of 5% glucose was administered preoperatively. Intravenous fluids during surgery consisted of 750 ml 5% glucose, 2800 ml lactated Ringer's solution, and 400 ml crystalloid. The patient's heart rate varied between 70 and 100 bpm, and his direct arterial pressure varied between 90/50 and 120/60 mmHg during the operation. Total operating time was 270 min. Reversal with atropine and neostigmine was brisk, and the trachea was extubated. The patient was fully alert and pain-free on arrival in the ICU. His postoperative course in the ICU was uneventful. Continuous epidural infusion of 5 μg·ml^{-1} of fentanyl with 0.25% bupivacaine for 1 day, 2.5 μg·$^{-1}$ of fentanyl with 0.125% bupivacaine for 1 day, and 0.25% bupivacaine for 2 days at a rate of 4 ml·h^{-1} was used successfully for postoperative analgesia. The perioperative urinary levels of porphyrins and precursor levels are summarized in Table 1. Compared to that before and during surgery, the coproporphyrin level increased after the operation on the 6th and 9th postoperative days, but no clinical symptoms of an acute attack were observed.

Discussion

Management of anesthesia in the patient with HCP is similar to that in AIP because acute attacks of HCP are triggered by the same factors as AIP [2]. The most important thing for the anesthetic management of a patient with HCP is to diagnose this condition preoperatively, because HCP is very rare and most patients are asymptomatic throughout their lives. There have also been conflicting reports regarding the safety of various drugs in patients with porphyrias [5]. Barbiturates are uniformly considered to be contraindicated in known porphyric patients [4]. However, several studies have revealed that patients with porphyria exposed to barbiturates for induction of general anesthesia did not develop and acute attack [10,11]. In the same study, some patients had worsening of porphyric symptoms after administration of barbiturates [11]. These results suggest that the administration of porphyrogenic drugs is probably only one of the factors that may precipitate a crisis; indeed, the determination of drug safety in anesthesia is further complicated by nonpharmacologic factors such as dehydration, infection, fever, and endogenous steroid hormones. Although barbiturates will not always precipitate a crisis, it is wise to avoid their use for induction of anesthesia in patients with known porphyria. We chose atropine for premedication; droperidol, fentanyl, nitrous oxide, and isoflurane for induction of anesthesia; and vecuronium as the muscle relaxant. Narcotics, anticholinergics, droperidol, and nitrous oxide are generally considered safe [1,5]. Muscle relaxants have been used extensively and are also generally considered to be safe [4]. However, the use of muscle relaxants with a steroid structure is questionable because steroid compounds are considered unsafe in porphyria [4]. Some reports have suggested that only pancuronium has been incriminated as unsafe based on data obtained from animals [12–14]. We chose vecuronium, and the its use was uneventful. Inhaled nitrous oxide and isoflurane were used for maintenance of anesthesia in this case. The safety of inhaled anesthetics in relation to porphyria is controversial. While Stoelting and Dierdorf have stated that inhaled anesthetics are safe [1], Jackson has pointed out that they are considered to be inducers of cytochrome P-450, and that this property would make them candidates for porphyrogenesis [4]. Experience with isoflurane is thus far limited, but recently some authors have reported this isoflurane was used in a patient with HCP without any deleterious clinical effect [8,9].

Since the frequent presence of autonomic nervous system dysfunction such as tachycardia, orthostatic hypotension, and hypertension is indicatd in patients with porphyria [1], strict perioperative monitoring

should be considered. Standard ECG, invasive arterial pressure via the radial artery, and central venous pressure were monitored perioperatively in this case, and the hemodynamic state was stable perioperatively. To avoid dehydration, which may precipitate crisis, intravenous fluids were administered at a basal rate of $10\,ml \cdot kg^{-1} \cdot h^{-1}$; additionally, 400 ml of crystalloid was given to compensate for blood loss.

Some authorities recommend that regional anesthesia be avoided because of the sporadic occurrence and unpredictable onset of central and peripheral neuropathological lesions in these patients [5]. However, the safe use of regional anesthesia has been reported in porphyria [6,7]. Carp and Clark have suggested that the use of regional anesthesia is not contraindicated as long as the possibility of autonomic dysfunction is considered [15]. In our patient, we used a continuous epidural infusion during surgery to avoid hemodynamic instability due to epidural anesthesia, because the possibility of labile blood pressure is always indicated in patients with porphyria [1]. In addition to pharmacologic factors, surgical stress and postoperative pain are also important factors that can trigger acute episodes of porphyria in surgical patients [1]. Taking these factors into consideration, we selected epidural anesthesia in this patient. Postoperatively, urinary coproporphyrin excretion transiently exceeded the upper normal limit. We were not able to determine the reason for this elevation because many factors contributed to it. We speculate that the epidural analgesia was effective in reducing not only surgical stress during operation but also postoperative pain, and that it resulted in the absence of acute attack. Parikh and Moore examined various agents in a rat model which suggested that procaine and bupivacaine are safe agents, but that lidocaine should be avoided [16]. There is no evidence that the use of bupivacaine in a regional anesthetic technique precipitates an attack of acute intermittent porphyria [6]. Epidural administration of a mixture of fentanyl and bupivacaine was effective for postoperative pain relief in our patient, without any complications.

To our knowledge this may be the first report in which general anesthesia with isoflurane, and epidural anesthesia with fentanyl and bupivacaine, were used safely in patient with HCP.

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