Original article **UDC: 616-008.9:616-089.5**

ANESTHETIC MANAGEMENT FOR A PATIENT WITH ACUTE INTERMITTENT PORPHYRIA

Angelina Bogićević[1], Lidija Đorđević[2], Biljana Stošić[1], Dragana Đorđević[1], Nenad Savić[1] and Anica Pavlović[1]

Acute intermittent porphyria is a rare metabolic disorder resulting from a partial deficiency of porphobilinogen deaminase, enzyme in the heme biosynthetic pathway. Its inheritance is autosomal dominant. A deficiency of porphobilinogen deaminase is not sufficient by its self to produce acute intermittent porphyria, and other activating factors must also be present. These include some drugs, hormones, infection, injury and alcohol.

Besides others, anesthetics have been implicated in the triggering of a number of severe porphyric reactions. Although there is no clinical evidence, the fear of hypothesized porphyrinogenicity of repetitive anesthetics exposures still remains. Despite these doubts, we report here the case of uneventful repeated exposure to anesthetics in a patient suffering from acute intermittent porphyria, within a fifteen- month period. On both occasions, the patient was safely exposed to certain anesthetics included: propofol, sevoflurane, rocuronium, midazolam and fentanyl. *Acta Medica Medianae 2010;49(3): 55-57.*

***Key words**: porphyria, anesthetics, complications*

Department of Anesthesia and Intensive Care, Surgery Clinic, Clinical Center Niš, Serbia [1]
Department for Endocrine Surgery, Surgery Clinic, Clinical Center Niš, Serbia[2]

Contact: Angelina Bogićević
Department of anaesthesia and reanimation
Surgery Clinic; Clinical Center Niš
Bulevar Dr Zorana Đinđića 48, 18 000 Niš
E-mail: angelina.bogicevic@gmail.com

Introduction

Acute intermittent porphyria (AIP) is a rare metabolic disorder resulting from a partial deficiency of porphobilinogen deaminase (PBGD), enzyme in the heme biosynthetic pathway. Its inheritance is autosomal dominant. Most people who inherit the gene for AIP never develop symptoms. A deficiency of PBGD is not sufficient by its self to produce AIP and other activating factors must also be present. In some people, however, certain factors can precipitate symptoms, producing an attack. Many drugs, sex hormones, low-calories and low-carbohydrate diets, ingestion of alcohol, mental stress or some infection are sometime implicated. Sometimes, the factors that cause an attack cannot be identified. Attacks are more common in women than in men, and occur only and very rarely before puberty. Symptoms may include acute onset of vomiting, abdominal or back pain, weakness in arms or legs, and mental symptoms, which are common, from irritation, restlessness, insomnia, and agitation to tiredness and depression.

Some authors suggested that repeated exposure to anesthetics may prove to be hazardous in acute intermittent porphyria (AIP) (1). With the exception of propofol, there are no published reports considering the safety of the repeated exposures to anesthetics in the patient suffering from AIP. Therefore, we report the case of repeated and prolonged exposure to certain anesthetics including: midazolam, propofol, rocuronium, fentanyl and sevoflurane in the same patient suffering from AIP.

Table 1. Anesthetic managements and total anesthetics consumption

Anesthetics	First anesthesia	Second anesthesia
Midazolam (mg)	7	7
Fentanyl (μg)	250	300
Rocuronium (mg)	60	100
Propofol (mg)	180	200
Sevoflurane (et vol. %)	1.6 - 2.5	1.3 – 2.8
Total anesthesia duration (min)	52	98

Case presentation

A 42-year-old female weighing 68 kg was primarily admitted for elective breast tumorectomy. After fifteen months, she had another medical procedure. This time, the procedure involved bilateral subcutaneous mastectomy together with primary reconstruction and implantation of breast implants (CPG Medium Gel Breast Implant Cohesive III a 355cc - Mentor®). Eleven years prior to the initial admission, she developed an acute quadriplegia following pregnancy, and was diagnosed as having an AIP. At the time of the admissions the patient was presented with the remaining bilateral peroneal paresis, but had no symptoms of an acute attack of porphyria. Her clinical condition was optimal. Examination of the urine for porphyrins confirmed the diagnosis of AIP – the Watson-Schwartz test was positive (+).

Both surgical procedures were performed under general anesthesia with similar managements (Table 1). Midazolam (0.1 $mg \cdot kg^{-1}$), used for pre-medication and rocuronium (0.6 $mg \cdot kg^{-1}$) were given under neuromuscular blockade monitoring (TOF Watch S–Organon Ireland LTD®) to facilitate endotraheal intubation and to provide the surgical relaxation. The first anesthesia was induced with fentanyl 150 μg and propofol 180 mg. In the same way, the following anesthesia was induced by fentanyl 200 μg and propofol 200 mg. On both occasions anesthesia was maintained by sevoflurane at an end-tidal concentration of 1.3–2.8% in 50% N_2O supplemented by intermittent boluses of fentanyl. Collectively, the patient received in total 380 mg of propofol and was exposed to continuous sevoflurane inhalation for the duration of 2.5 hours. Postoperative analgesia was provided by ketorolac 30 mg every 6 hours. The patient was supplied with sufficient amounts of glucose solutions in order to avoid a hypoglycemic state during perioperative and early postoperative period. Both perioperative courses were uneventful, the patient exhibited no signs of an acute porphyric crisis and was discharged home as per routine.

Discussion

AIP is an autosomal dominant disorder of heme biosynthesis caused by molecular defects in the porphobilinogen (PBG) deaminase gene which then lead to the accumulation of the heam precursors: PBG and δ-aminolaevulinic acid (ALA). Besides others, anesthetics have been implicated in the triggering of a number of severe porphyric reactions. Although there is no clinical evidence, the fear of hypothesized porphyrinogenicity of repetitive anesthetics exposures still remains.

Propofol is considered, being safe as a drug for both induction and for maintenance of anesthesia for patients with AIP (1). Although some reports showed elevated porphyrins following continuous infusions or repeated propofol exposure, this was not accompanied by any porphiric symptoms. In the aforementioned, total doses of 900 and 1300 mg of propofol were administered (2,3). Opposite to those findings, *Shaw* and *McKeith* presented the course of uneventful electroconvulsive treatments with propofol as the sole induction agent. In seven repetitive treatments, the patient received in total 450 mg of propofol within 23-day period with no urinary porphirins detected (4). On the other hand, the safe repetitive exposures to propofol were presented likewise by the *Mitter-schiffthaller et al.* (5) and *Harrison and McAuley* (6). Considering all these findings, there remain some doubts about the safety of repeated or prolonged exposure to propofol to the patients suffering from AIP. We uneventfully administered the total 380 mg of propofol on two occasions in the same patient.

Recently Hsieh et *al*. reported the safe use of rocuronium in AIP (7). It was the first ever reported use of rocuronium in this specific occasion. Some authors postulated that as with propofol, prolonged use of rocuronium may not be safe (1). Nevertheless, our patient received on both occasions a total of 160 mg of rocuronium with no clinical or laboratory evidence of its porphyrinogenicity.

Modern inhalation agents are generally considered safe in porphyric patients. Sevoflurane has been reported as a safe agent for both induction and maintenance of anesthesia (7-9). Fast and relatively unchanged elimination and the minimal induction of the cytochrome P 450 system render sevoflurane favorable in this back-ground. On the contrary, the animal studies strongly suggested a significant induction in ALA-synthase activity and a reduction of PBG-ase activity following administration of volatile anesthetics, which included sevoflurane (10). We safely exposed our patient to repeated sevoflurane inhalation which lasted 2.5 hours. Our clinical experience supports the opinion that both cell culture and animal models tend to overestimate the porphyrinogenicity of investigated drugs (1).

Literature on midazolam and any of the opiates currently in use suggest they can safely be used in AIP (1).

Some limitations of our conclusion may be derived from insufficient laboratory investigations. Regrettably, the semi quantitative Watson-Schwartz test for porphyria is only available in our hospital.

In conclusion, in spite of uncertainties that repeated or prolonged exposure to ane-sthetics may be hazardous in a case of AIP, we suggest that certain anesthetics such as midazolam, propofol, rocuronium, fentanyl and sevoflurane might be safely used on repetitive occasions in the same patient with AIP.

References

1. James MFM, Hift RJ. Porphyrias. Br J Anaesth 2000; 85:143–53.
2. Meissner PN, Harrison GG, Hift RJ. Propofol as an i.v. anaesthetic induction agent in variegate porphyria. Br J Anaesth 1991;66(1):60-5.
3. Elcock D, Norris A. Elevated porphyrins following propofol anaesthesia in acute intermittent porphyria. Anaesthesia 1994;49(11):957-8.
4. Shaw IH, McKeith IG. Propofol and electroconvulsive therapy in a patient at a risk from acute intermitente porphyria. Br J Anaesth 1998;80(2):260-2.
5. Short CE, Bufalari A. Propofol anesthesia. Vet Clin North Am Small Anim Pract. 1999 May;29(3):747-78.
6. Mehta M, Rath GP, Padhy UP, Marda M, Mahajan C, Dash HH. Intensive care management of patients with acute intermittent porphyria: Clinical report of four cases and review of literature. Indian J Crit Care Med. 2010; 14(2):88-91.
7. Harrison JC, McAuley FT. Propofol for sedation in intensive care in a patient with an acute porphyric attack. Anaesthesia 1992;47(4):355-6.
8. Hsieh CH, Hung PC, Chien CT, Shih YR, Peng SK, Luk HN, et al. The use of rocuronium and sevoflurane in acute intermittent porphyria - a case report. Acta Anaesthesiol Taiwan 2006;44(3):169-71.
9. Evans PR, Graham S, Kumar CM. The use of sevoflurane in acute intermittent porphyria. Anaesthesia 2001;56(4):388-9.
10. Takahashi S, Shiraishi Y, Yokoyama J. A case report of rapid inhalation induction with sevoflurane in a patient with porphyria. Masui 2005;54(11):1292-4.
11. Buzaleh AM, Garcıa-Bravo M , Navarro S, Moran-Jimenez MJ, Mendez M, Batlle A, et al. Volatile anaesthetics induce biochemical alterations in the heme pathway in a B-lymphocyte cell line established from hepatoerythropoietic porphyria patients (LBHEP) and in mice inoculated with LBHEP cells. Int J Biochem Cell Biol 2004;36(2):216–22.

SPECIFIČNOSTI ANESTEZIJE KOD BOLESNIKA OBOLELIH OD AKUTNE INTERMITENTNE PORFIRIJE

Angelina Bogićević, Lidija Đorđević, Biljana Stošić, Dragana Đorđević, Nenad Savić i Anica Pavlović

Akutna intermitentna porfirija je redak, autozomno dominantno nasledni metabolički poremećaj, u čijoj je osnovi poremećaj biosinteza hema. Uslovljena je nedostatkom enzima porfobilinogen deaminaze, što za posledicu ima nagomilavanje prekursora hema: porfobilinogena i δ-aminolevulinske kiseline. Sam nedostatak enzima nije dovoljan za pojavu bolesti, jer sem toga moraju biti prisutni i drugi, aktivirajući faktori. Najčešće se pominju određeni lekovi, hormoni, infekcija, povrede, gladovanje, alkohol i razni toksini.

Između ostalih, anesteticima se pripisuje svojstvo okidača teških porfirijskih reakcija. Iako ne postoje čvrsti klinički dokazi, strah od pretpostavljenog uticaja ponavljanih ili produženih izlaganja anesteticima kod bolesnika obolelih od porfirije još uvek postoji. Nasuprot tome, u ovom članku mi prikazujemo slučaj bezbedne ponovljene ekspozicije anesteticima u vremenskom razmaku od petnaest meseci kod bolesnice sa dokazanom akutnom intermitentnom porfirijom. Obe hirurške procedure su izvedene u opštoj anesteziji, sa sličnom strategijom. Od anestetika su korišćeni: propofol, sevofluran, rokuronijum, midazolam i fentanil. *Acta Medica Medianae 2010;49(3):55-57.*

***Ključne reči**: porfirija, anestezija, komplikacije*