Clinical case

doi: 10.35366/99671

Revista Mexicana de Anestesiología
July-September 2021
Vol. 44. No. 3. pp 229-232

Use of sugammadex in acute intermittent porphyria

Uso de sugammadex en la porfiria aguda intermitente

Joana Tinoco, M.D.,* André Eloy, M.D.,* Rita Regufe, M.D.,*
Daniela Rosinha, M.D.,* Tiago Taleco, M.D.,* João Silva-Duarte, M.D.*

How to cite: Tinoco J, Eloy A, Regufe R, Rosinha D, Taleco T, Silva-Duarte J. Use of sugammadex in acute intermittent porphyria. Rev Mex Anestesiol. 2021; 44 (3): 229-232. https://dx.doi.org/10.35366/99671

ABSTRACT. Porphyrias are a group of rare diseases, which include acute intermittent porphyria. It is essential for the anesthesiologist to identify acute porphyrias and to recognize a porphyric crises. These can be triggered by several factors, which can be present throughout the perioperative period. A 70-year-old male, ASA III, with a personal history of acute intermittent porphyria and ischemic heart disease, scheduled for laparoscopic sigmoidectomy. Prolonged fasting, dehydration and potentially porphyrinogenic drugs were avoided. General anesthesia was induced with fentanyl, lidocaine, propofol and rocuronium and maintained with desflurane. The decision to reverse the neuromuscular blockade with sugammadex was considered due to the benefits over risks of this drug when compared to neostigmine (associated with atropine) and the description of its use without harm in two cases of variegate porphyria. The following paper emphasize the importance of careful anesthetic management throughout the perioperative period and describe a case of successful reversal of neuromuscular block with sugammadex, highlighting this case as the first case reported of its use in acute intermittent porphyria.

RESUMEN. *Las porfirias son un grupo de enfermedades raras, entre las que se encuentra la porfiria aguda intermitente. Es fundamental que el anestesista identifique las porfirias agudas y reconozca una crisis porfírica. Éstos pueden ser desencadenados por varios factores, que pueden estar presentes durante todo el periodo perioperatorio. Varón de 70 años, ASA III, con antecedentes personales de porfiria aguda intermitente y cardiopatía isquémica, programado para sigmoidectomía laparoscópica. Se evitó el ayuno prolongado, la deshidratación y los fármacos potencialmente porfirinógenos. La anestesia general se indujo con fentanilo, lidocaína, propofol y rocuronio y se mantuvo con desflurano. La decisión de revertir el bloqueo neuromuscular con sugammadex se consideró debido a los beneficios sobre los riesgos de este fármaco en comparación con la neostigmina (asociada con la atropina) y a la descripción de su uso sin daños en dos casos de porfiria variegada. El siguiente artículo enfatiza la importancia de un manejo anestésico cuidadoso durante todo el periodo perioperatorio y describe un caso de reversión exitosa del bloqueo neuromuscular con sugammadex, destacando este caso como el primero reportado de su uso en porfiria aguda intermitente.*

Keywords:
Sugammadex, acute intermittent porphyria, anesthesia management, case report.

Palabras clave:
Sugammadex, porfiria intermitente aguda, manejo de la anestesia, informe de caso.

* Department of Anesthesiology, Setúbal Hospital Center, São Bernardo Hospital, Portugal.

Correspondence:
Joana Tinoco, M.D.
E-mail: joana.tinoco@hotmail.com

Received: 03-03-2020
Accepted: 29-09-2020

INTRODUCTION

Porphyrias represent a group of rare metabolic diseases, which derive from enzymatic deficiencies in heme biosynthesis of the hemoglobin chain. Depending on the affected enzyme, there will be an accumulation of toxic and different porphyrin precursors that will originate the respective form of the disease. Classically, porphyrias are divided into acute porphyrias and cutaneous porphyrias[1,2].

Acute intermittent porphyria is a dominant autosomal disease, characterized by deficiency of the porphobilinogen deaminase enzyme. Despite its heredity, family history may be absent in some cases due to a low penetrance[3].

The main symptoms are porphyric crises, essentially characterized by neurovisceral symptoms, which can pose the greatest challenge for the anesthesiologist, due to the diversity of acute trigger factors that can be present throughout the perioperative period: emotional/physical stress, fasting, dehydration, hypoglycemia and drugs[4,5].

There is a lack of published information about the use of sugammadex and its safety in this group of patients, and this article aims to contribute to change this situation by reporting the reversal of neuromuscular blockade with sugammadex in a patient with acute intermittent porphyria.

CASE DESCRIPTION

A 70-year-old male patient, ASA III, 100 kg, was proposed for elective laparoscopic sigmoidectomy for diverticular disease.

In addition to acute intermittent porphyria, he presented: arterial hypertension, acute myocardial infarction in 2004 with coronary stent placement, moderate obstructive sleep apnea syndrome (no APAP adhesion), benign prostatic hypertrophy and grade I obesity. He had no drug allergies and was only taking acetylsalicylic acid 100 mg daily.

The patient described sporadic crises since the age of 18, with mild and nonspecific symptoms (sudden asthenia, mild to moderate abdominal pain, nausea and vomiting) that resolved in 2 to 3 days only with supportive therapy. The formal diagnosis was made in 1996, following a severe acute crisis of his youngest son that motivated enzymatic assays and genetic studies.

He had undergone four surgeries (2 urologic and 2 orthopedic), all uneventful.

In the pre-anesthetic assessment, he presented no exacerbation of his conditions and the exams requested were within normal range.

He was scheduled for the first operative time to minimize the fasting, during which, he was maintained on an infusion of glycated polyelectrolyte to avoid caloric restriction and dehydration.

In the operating room, noninvasive standard monitoring and anesthetic depth with BIS and neuromuscular block monitoring were maintained.

General anesthesia was induced with 2 µg/kg fentanyl, lidocaine 1 mg/kg, propofol 2 mg/kg and Rocuronium 0.6 mg/kg. Anesthesia was maintained with desflurane and incremental bolus of rocuronium were given (in total 125 mg). During procedure the patient received 100 µg of fentanyl, 1 g of paracetamol and 2 mg of morphine. Post-operative nausea and vomiting was prevented with droperidol 0.625 mg and ondansetron 4 mg. During the surgery hypothermia was prevented with a forced air patient warming device and fluid warmers.

The surgery lasted for 4 hours, with no relevant events. The surgical incisions were infiltrated with 5 mg/mL bupivacaine.

Neuromuscular block was reversed with and sugammadex at a dose of 2 mg/kg (200 mg), according to TOF count and the patient extubated.

During the stay at the post-anesthetic care unit, a patient-controlled analgesia protocol with bolus morphine was chosen, with 1 g paracetamol every 6 hours. The patient was then transferred to an intermediate surgical care unit and was discharged on the 5th postoperative day.

DISCUSSION

Porphyrias can be classified in hepatic or erythropoietic, whether the accumulation of porphyrin precursors occurs in

Table 1: Recommendations regarding the prescription of drugs commonly used in clinical practice and the respective porphyrinogenic risk.

	Not porphyrinogenic	Probably not porphyrinogenic	Possibly porphyrinogenic	Probably porphyrinogenic	Porphyrinogenic	Still without classification
Anesthetics	Propofol	Midazolam, desflurane, sevoflurane, nitrous oxide	Dexmedetomidine, ketamine		Etomidate, thiopental	
Analgesics	Morfine, meperidine, pethidine	Fentanyl, remifentanil, alfentanil, sufentanil, acetaminophen, tramadol, ketorolac, diclofenac, ibuprofen, parecoxib		Metamizole		
Local anesthetics	Bupivacaine	Levobupivacaine, ropivacaine, lidocaine				
Muscle relaxants	Rocuronium, cisatracurium, suxamethonium	Atracurium, vecuronium				Dantrolene
Neuromuscular blockade reversers		Sugammadex, neostigmine, glycopyrrolate, pyridostigmine				
Antiemetics, antacids	Omeprazole	Ondansetron, droperidol, metoclopramide, esomeprazole, ranitidine	Dexamethasone			
Vasopressors, positive ionotropic and chronotropic drugs	Ephedrine, dopamine, adrenaline, noradrenaline	Phenylephrine				Isoprenaline
Antihypertensive, negative ionotropic and chronotropic drugs	Propranolol, esmolol, labetalol, isosorbide, dinitrate, digoxin, adenosine	Nifedipine		Methyldopa, hydralazine	Methyldopa, hydralazine	
Others	Intralipid, tranexamic, acid	Naloxone	Flumazenil, hydrocortisone			Clemastine

Porphyrinogenic: prescribe only in urgent situations, with precautions in all cases; **probably porphyrinogenic:** prescribe only in strong and urgent indications; **possibly porphyrinogenic:** use only in the absence of safer alternatives; **probably not porphyrinogenic e not porphyrinogenic:** use as first choice. Adapted from references 6 to 8.

the liver or the bone marrow[5], or classified based on clinical characteristics, in acute or cutaneous.

Porphyrias are rare diseases. The estimated prevalence in Europe of acute intermittent porphyria is about 1/20,000[5]. This acute form, consisting in deficiency of porphobilinogen-deaminase, has a hereditary autosomal dominant transmission pattern. Despite hereditary transmission, family history may be absent due to a low penetrance rate of the disease[3].

It is essential for the anesthesiologist to identify acute forms and recognize their clinical presentation. Acute crises carry a high mortality risk if they are not quickly addressed and can be triggered by several factors, which can be present during the perioperative period.

Porphyria crisis may include signs and symptoms such as abdominal pain, nausea and vomiting, diarrhea, autonomic nervous system instability, tachycardia, arterial hypertension, muscle weakness (in 20% of cases it can lead to respiratory failure), anxiety, agitation, hallucinations and seizures[4,5].

The most frequent triggering factors are dehydration, fasting, hypoglycemia, infections, emotional and physical stress, hormonal changes and drugs[4].

The anesthetic management should be carefully planned, emphasizing the importance of choosing the safest drugs. Websites of accredited international entities with specific lists of safe and unsafe drugs for patients with porphyria are available on the internet, including: 1) European Porphyria Network, 2) American Porphyria Foundation e 3) The Norwegian Porphyria Centre (NAPOS)[6-8].

We have drugs with specific contradictions in the above-mentioned lists. On the other hand, some drugs have an unknown risk, due to lack of scientific studies to prove their safety. *Table 1* was produced from the database of the international entities mentioned above and represents their most recent recommendations for the drugs daily administered in the anesthetic clinical practice[6-8].

Regarding the anesthetic management, we opted on general anesthesia, since volatile agents are considered relatively safe (probably not porphyrinogenic). However, total intravenous anesthesia with perfusion of propofol has also been described as a safe alternative[9,10].

For the post-operative analgesia, the patient's medical history was considered. Non-steroidal anti-inflammatory drugs were ruled out due to history of cardiac ischemic disease. Opioids were administered intraoperatively and postoperatively as they ensure effective analgesia.

Rocuronium was chosen as the neuromuscular agent, because it is totally non-porphyrinogenic. Complete reversal of blockade with minimal cholinergic and cardiovascular effects (undesirable due to the patient's cardiac history) was desirable, so we considered the benefits over risks of using sugammadex, that at the date had not yet been evaluated for its porphyrinogenic risk. This drug allows neuromuscular block reversal with greater efficacy (less incidence of residual blockade), speed (dose adjustable to the intensity of the neuromuscular blockade), and with fewer side effects when compared to the association of neostigmine and atropine (the option we have in our hospital). Due to being a recent drug, there is sparse information about its use in porphyria. On our case, we chose to dilute and administer it slowly in order to allow the recognition of any immediate complications.

At the time of this procedure, sugammadex safety profile hadn't been evaluated on any list due to lack of available information. Currently, NAPOS has classified it as «probably not porphyrinogenic» for the acute forms of porphyria[8]. This classification is justified by the fact that sugammadex is a modified gamma-cyclodextrin compound, used to reverse rocuronium's and vecuronium's neuromuscular blockade, through the formation of complexes by encapsulation of the neuromuscular agent molecules. It is pharmacologically proven that sugammadex is not metabolized by the liver, it is eliminated in intact form or in the form of complexes by the kidney. An insignificant part can also be eliminated in the feces[11].

The literature review, using the keywords «porphyria» and «sugammadex», only allowed to find three case reports on the use of sugammadex in this group of diseases: two cases in patients with variegate porphyria[12,13] and one case in a patient with porphyria cutanea tarda[10]. In all cases the use of this drug revealed no complications, and all concluded that its use is relatively safe[10,12,13].

The presented clinical case is the first one to report the successful use of sugammadex in a patient with acute intermittent porphyria.

CONCLUSION

Anesthetic management of this patients should be planned in the pre-anesthetic evaluation, emphasizing the importance of our management, from the time of admission to hospital discharge. It is extremely important that the anesthesiologist knows how to recognize the factors triggering acute attacks, as well as minimizing their impact.

Based on information published in other clinical cases, the use of sugammadex is probably safe in patients with porphyria, highlighting this case as the first case reported of its use in acute intermittent porphyria.

Consent for publication: Written informed consent to publish this case report was obtained from the patient.

Conflict of interest: The authors declare that they have no conflict of interest.

REFERENCES

1. Stein PE, Badminton MN, Rees DC. Update review of the acute porphyrias. Br J Haematol. 2017;176:527-538.
2. Ajayi T, Ward R, Summers B, et al. Pathophysiology, pharmacology and treatment of acute intermittent porphyria: a patient case description and recommendations from the current literature. J Explor Res Pharmacol. 2017;2:49-53.
3. Sood GK, Anderson KE. Pathogenesis, clinical manifestations, and diagnosis of acute intermittent porphyria. Waltham, MA: Walters Kluwer Health; 2019. [Accessed July 29, 2019] Available in: https://www.uptodate.com/contents/acute-intermittent-porphyria-pathogenesis-clinical-features-and-diagnosis
4. Findley H, Philips A, Cole D, et al. Porphyrias: implications for anaesthesia, critical care, and pain medicine. Contin Educ Anaesth Crit Care Pain. 2012;12:128-133.
5. Ramanujam VS, Anderson KE. Porphyria diagnostics-Part 1: a brief overview of the porphyrias. Curr Protoc Hum Genet. 2015;86:17.20.1-17.20.26.
6. European Porphyria Network. [Accessed September 29, 2019] Available in: www.drugs-porphyria.org
7. American Porphyria Foundation. [Accessed September 29, 2019] Available in: http://www.porphyriafoundation.com/drug-database
8. The Norwegian Porphyria Centre (NAPOS). [Accessed September 29, 2019] Available in: http://www.drugs-porphyria.org/
9. Kuźminski A, Aporowicz M, Brol M, et al. Elective cholecystectomy performed on patient with variegate porphyria-propofol based total intravenous anesthesia with target-controlled infusion. J Clin Anesth. 2016;35:114-117.
10. Crespo S, Herrero M. Anestesia general en pacientes con porfiria. Revista Electrónica de AnestesiaR (RealR). 2018;10:1. [Accessed October 2, 2019] Disponible en: http://revistaanestesiar.org/index.php/rear/article/view/48
11. Nag K, Singh DR, Shetti AN, et al. Sugammadex: a revolutionary drug in neuromuscular pharmacology. Anesth Essays Res. 2013;7:302-306.
12. Buijs E, Scholten J, Ros J. Successful administration of sugammadex in a patient with acute porphyria – A case report. Eur J Anaesthesiol. 2014;31:439-441.
13. Aoki Y, Atsumi K, Kora M, Koh N, Yokoyama J. Sugammadex and amino acid infusion can contribute to safe anesthetic management of variegate porphyria. JA Clin Rep. 2018;4:49.