Use of sugammadex in acute intermittent porphyria

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.*


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 porphyrine crisis. 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.

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 porphryic 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 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

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<thead>
<tr>
<th>Table 1: Recommendations regarding the prescription of drugs commonly used in clinical practice and the respective porphyrinogenic risk.</th>
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<tbody>
<tr>
<td><strong>Not porphyrinogenic</strong></td>
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<tr>
<td>Anesthetics</td>
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<tr>
<td>Analgesics</td>
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<tr>
<td>Local anesthetics</td>
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<td>Muscle relaxants</td>
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<tr>
<td>Neuromuscular blockade reversers</td>
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<td>Antiemetics, antacids</td>
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<td>Vasopressors, positive ionotropic and chronotropic drugs</td>
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<tr>
<td>Anthypertensive, negative ionotropic and chronotropic drugs</td>
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<tr>
<td>Others</td>
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**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\(^8,10,12,13\).

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