

Anaphylaxis to sugammadex: A rare yet critical perioperative challenge

Anafilaxia a sugamadex: Um caso raro de hipersensibilidade perioperatória grave

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André Justino Alberto¹ , Ana Raquel Pinto¹ , Eva Rebelo Gomes¹ 

¹ Allergy and Clinical Immunology Department, Unidade Local de Saúde de Santo António, Porto, Portugal

Author contributions: André Alberto: Investigation, writing – original draft preparation; Ana Raquel Pinto: Investigation, writing – original draft preparation; Eva Rebelo Gomes: Conceptualization, investigation, writing – review & editing

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ABSTRACT

The allergological evaluation of perioperative hypersensitivity reactions is challenging due to the simultaneous administration of multiple drugs and the hemodynamic effects of anesthesia and surgery. Sugammadex has been increasingly reported as a perioperative trigger. The incidence of perioperative anaphylaxis varies geographically across Europe, ranging from 1:1,250 to 1:18,600 procedures. We report the case of a 23-year-old woman who underwent cesarean section under epidural anesthesia, later converted to general anesthesia. Immediately after sugammadex administration, she developed grade III anaphylaxis, successfully treated with intramuscular adrenaline, intravenous hydrocortisone, and clemastine. Due to the severity of the reaction, the diagnostic investigation began with in vitro testing. A basophil activation test was positive for sugammadex at 2.5 mg/mL. Subsequent intradermal tests were positive for the same agent at 1 and 10 mg/mL, corroborating the basophil activation test result. Avoidance of sugammadex and chemically related compounds was recommended. This case highlights the importance of considering sugammadex as a potential trigger in perioperative anaphylaxis.

Keywords: Allergy diagnosis, anesthesia, basophil activation test, drug hypersensitivity, perioperative anaphylaxis, sugammadex.

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RESUMO

A avaliação alergológica das reações de hipersensibilidade perioperatórias é um desafio devido à administração simultânea de múltiplos fármacos e aos efeitos hemodinâmicos da anestesia e da cirurgia. O sugamadex tem sido descrito de forma crescente como um fármaco implicado em reações de anafilaxia perioperatória. A incidência de anafilaxia perioperatória varia geograficamente na Europa, ocorrendo em cerca de 1:1.250 a 1:18.600 procedimentos. Apresentamos o caso de uma mulher de 23 anos submetida a cesariana sob anestesia epidural, posteriormente convertida para anestesia geral. Imediatamente após a administração de sugamadex, desenvolveu anafilaxia grau III, tratada com sucesso com adrenalina intramuscular, hidrocortisona intravenosa e clemastina. Devido à gravidade da reação, a investigação diagnóstica iniciou-se por testes *in vitro*. O teste de ativação dos basófilos foi positivo para sugamadex na concentração de 2,5 mg/mL. Posteriormente, os testes intradérmicos foram positivos para o mesmo agente nas concentrações de 1 e 10 mg/mL, corroborando o resultado do teste de ativação dos basófilos. Foi recomendada a evicção de sugamadex e de compostos quimicamente relacionados. Este caso reforça a importância de considerar o sugamadex como potencial desencadeante de anafilaxia perioperatória.

Palavras-chave: Anafilaxia perioperatória, anestesia, diagnóstico alergológico, hipersensibilidade a medicamentos, sugamadex, teste de ativação dos basófilos.

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The allergological study of perioperative hypersensitivity poses numerous challenges, including the simultaneous administration of multiple drugs and their pharmacological effects, as well as the hemodynamic changes resulting from the anesthetic and surgical intervention itself. The incidence of perioperative anaphylaxis varies geographically, ranging from 1:1250 to 1:18600 procedures involving general anesthesia (1-2). The most involved agents are neuromuscular blocking agents (NMBAs), antibiotics, chlorhexidine, and latex. However, other frequently used drugs cannot be reliably excluded based solely on clinical history (2).

NMBAs are the most common cause of perioperative hypersensitivity in several European countries, including France, Norway, and Belgium (2). Sugammadex, the first selective relaxant binding agent (SRBA) approved by the FDA (3), is widely used to reverse NMBAs-induced neuromuscular blockade, particularly that caused by rocuronium. Its mechanism of action involves encapsulating the

NMBA molecule to form a stable complex, thereby neutralizing its effect. Compared to previously available reversal agents, sugammadex has fewer muscarinic side effects and can reverse deep neuromuscular blockade in a dose-dependent manner, making it a particularly attractive option in such settings (4). Since the first reported case of sugammadex-induced anaphylaxis in 2011, an increasing number of cases have been described (3).

We report the case of a 23-year-old woman who underwent a cesarean section under combined spinal-epidural anesthesia, which was converted to general anesthesia due to an insufficient blockage for the cesarean procedure. A few minutes after administration of sugammadex, she developed a generalized maculopapular exanthema, lip angioedema, tachycardia (135 bpm), and hypotension (74/41 mmHg). Anaphylaxis (Grade III) (5) was suspected, and she promptly started treatment with intramuscular adrenaline, intravenous hydrocortisone, and clemastine, with symptom resolution in minutes.

Given the severity of the reaction, the diagnostic work-up was initiated with *in vitro* testing. Laboratory analysis revealed a total IgE level of 40 kU/L and a baseline serum tryptase of 2.66 µg/L, compared to an acute-phase tryptase of 16.4 µg/L. A basophil activation test (BAT) was performed using rocuronium and sugammadex tested separately (without the rocuronium-sugammadex complex). A positive response was observed for sugammadex at 2.5 mg/mL, with CD63 expression in 6.17% of activated basophils and a stimulation index of 9.35 (Figure 1) while

rocuronium testing was negative. Subsequently, skin prick (SPT) and intradermal tests (IDT) were performed with lidocaine, bupivacaine, fentanyl, sufentanil, rocuronium, sugammadex and chlorhexidine using EAACI-recommended concentrations (2). IDT was positive for sugammadex at concentrations of 1 and 10 mg/mL (Figure 2). A subcutaneous provocation test with lidocaine was negative.

Sugammadex was thus considered the culprit drug, and strict avoidance, along with avoidance of structurally related compounds, was recommended. Regarding the

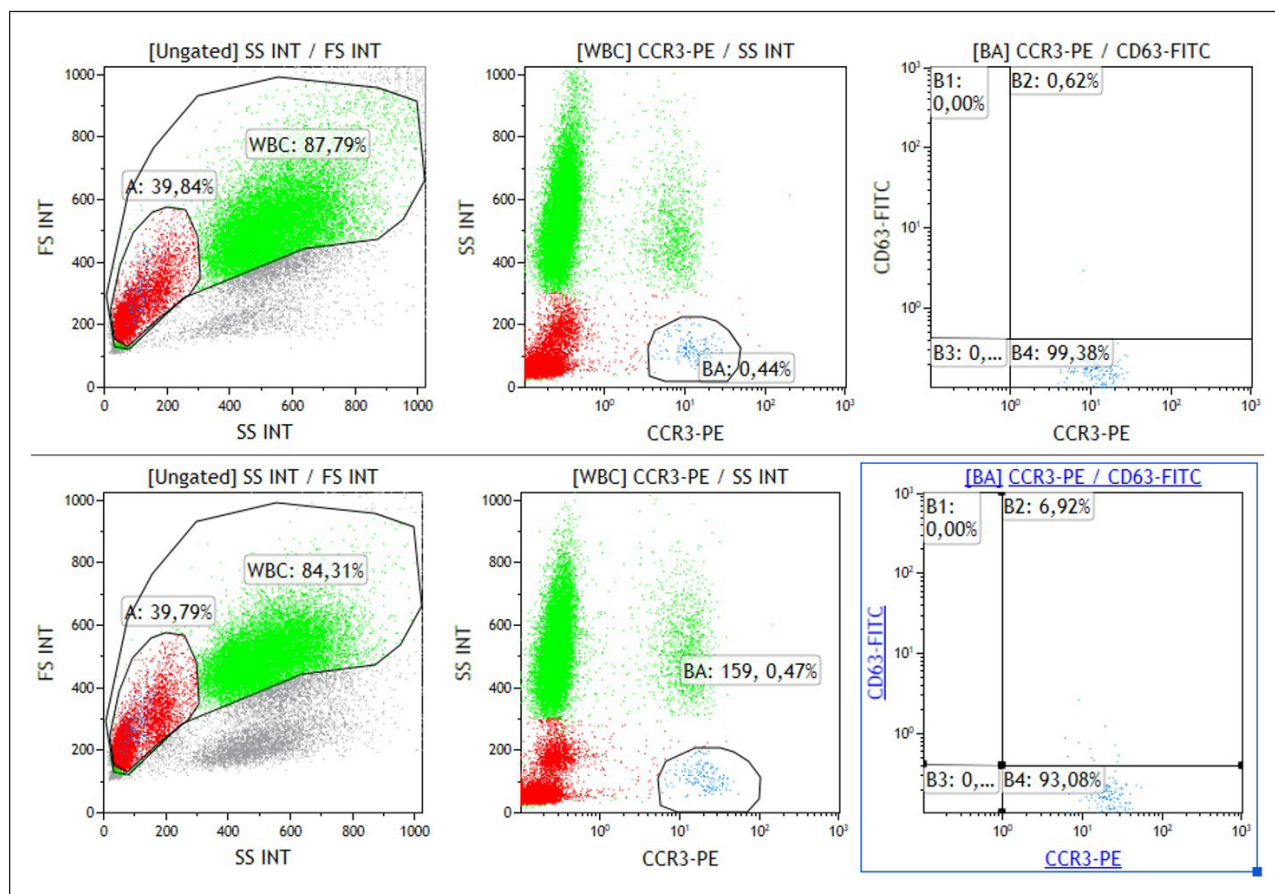


Figure 1: Flow cytometry basophil activation test results using negative control (top row) and sugammadex at a concentration of 2.5 mg/mL, dilution 1/40 (bottom row). The first vertical row displays scatterplots of cells, with forward scatter (FS, x-axis) indicating cell size and side scatter (SS, y-axis) indicating cell granularity; here we observe the selection of the total leukocyte population (WBC, in green). The second vertical row depicts SS against CCR3 expression, where the basophil population is identified within a specific gate (BA, also in green, on the right upper quadrant). Lastly, the third vertical row shows the gated basophil population, labeled with CD63, a marker of cell activation (B2) showing 0.62% for the negative control and 6.92% for sugammadex.

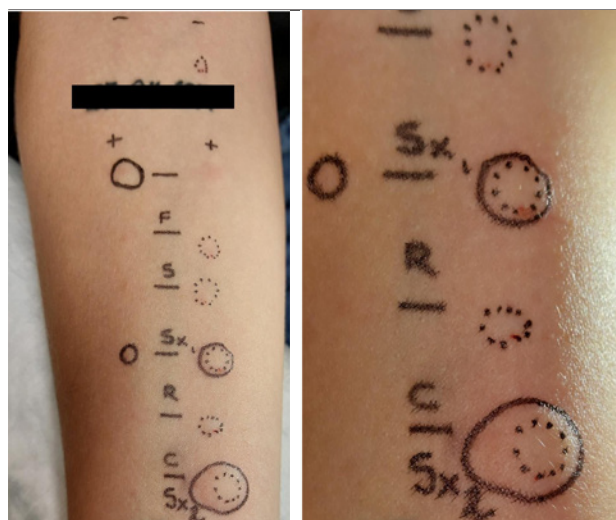


Figure 2. Skin prick tests (left side on both images) and intradermal tests (right side on both images), with positive results for sugammadex in 1:1 (Sx2) and 1:10 (Sx1) concentrations.

remaining agents, their eventual re-administration would only be advisable in the hospital setting, with close anesthetic supervision.

This case emphasizes the importance of including sugammadex in the differential diagnosis of perioperative anaphylaxis and supports the utility of BAT as a safe and effective diagnostic approach in severe drug allergy cases.

A review by Arslan *et al.* analyzing 33 cases of sugammadex-induced anaphylaxis found that, although the number of reported hypersensitivity reactions remains relatively low, the most common clinical manifestations include tachycardia, erythema, hypotension, and oxygen desaturation. In most cases, symptoms appeared within the first five minutes following administration (4).

Basophil activation can be assessed using markers such as CD63 and CD203c. Horiuchi *et al.* reported a sensitivity of 75% and specificity of 100% for BAT employing CD63 in the diagnosis of sugammadex hypersensitivity (6). In our case, BAT was used to detect *in vitro* reactivity, allowing us to initially avoid *in vivo* testing. However, since BAT is not yet fully standardized, the patient consented to undergo SPT and IDT, which were positive and served to corroborate the BAT results.

The increasing number of reported perioperative anaphylaxis cases highlights the importance of heightened awareness among anesthesiologists, allergists, and perioperative teams regarding the potential for sugammadex-induced anaphylaxis. Given its widespread use and favorable safety profile, delayed recognition of hypersensitivity reactions can have serious consequences.

Incorporating BAT into diagnostic algorithms for perioperative hypersensitivity may facilitate early identification of the culprit drug, reduce diagnostic uncertainty, and prevent unnecessary exclusion of essential anesthetic agents. Expanding access to BAT and promoting standardized testing protocols across centres may further improve diagnostic accuracy and patient outcomes, particularly when skin testing is contraindicated or inconclusive.

Further studies are needed to strengthen the evidence base. Nevertheless, BAT appears to be a promising first-line diagnostic tool in suspected cases of sugammadex-induced anaphylaxis, offering a safer alternative to *in vivo* testing.

KEY MESSAGE

We underscore the significance of considering sugammadex as an agent involved in perioperative hypersensitivity reactions, as well as the importance of allergological studies in these cases to provide more precise recommendations in the event of future surgical interventions.

Conflicts of interest

The authors disclose they have no conflicts of interest.

ORCID

André Justino Alberto  0000-0001-9041-1708

Ana Raquel Pinto  0000-0002-1505-105X

Eva Rebelo Gomes  0000-0001-8956-9145

Corresponding author

André Manuel Justino Alberto 

Rua Prof. Vicente José de Carvalho 37, 4050-366 Porto

E-mail: amj.alberto@gmail.com

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