

duration of prophylaxis (Table 1). This is consistent with recent recommendations for monitoring provided by the Australian Commission on Safety and Quality in Healthcare Antimicrobial Stewardship Clinical Care Standard⁶. It is paramount that accurate data be collected with available resources and be interpretable as 'data for action' at the hospital level⁷, facilitating the structuring and implementation of targeted antimicrobial stewardship and infection prevention programs.

Table 1

Required elements for generation of effective quality indicators of surgical antibiotic prophylaxis

- Hospital-level data must be obtained using existing resources.
- Reporting by surgical procedure group category.
- Data must be valid and reproducible.
- Periodic or continuous auditing may be performed according to available hospital resources and objectives of the monitoring program.
- Monitoring should include choice, timing*, and duration of prophylaxis.
- Assessment of appropriateness must be based upon available evidence or consensus opinion of experts.
- Data must be relevant and interpretable by all stakeholders, particularly clinical staff.
- Facilities monitoring surgical antibiotic prophylaxis should also consider monitoring surgical site infections using standardised surveillance methods.

*Including repeat dosing for prolonged surgical procedures.

A. L. Bull
K. A. Thursky
M. J. Richards
L. J. Worth
Melbourne, Victoria

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Anaphylaxis to sugammadex diagnosed by skin prick testing using both sugammadex and a sugammadex-rocuronium mixture

Sugammadex, a rapid and effective reversal agent of rocuronium and vecuronium, is widely used in many countries. However, cases of anaphylaxis to clinical doses of sugammadex have been reported¹⁻³. Sugammadex binds to rocuronium, forming a sugammadex-rocuronium complex immediately after intravenous administration. Thus, distinguishing between free sugammadex and a sugammadex-rocuronium complex as the trigger for anaphylaxis immediately after the administration of sugammadex is clinically important. Here we report a case of anaphylaxis to sugammadex diagnosed by skin prick testing using both sugammadex alone and a sugammadex-rocuronium mixture. Written consent for publication was obtained from the patient.

A 60-year-old, 50 kg woman underwent craniotomy for suspected meningioma. The patient had no history of allergy or previous sugammadex administration. Anaesthesia was induced with propofol and remifentanyl. Muscle relaxation was achieved with rocuronium. During surgery, fentanyl, lignocaine, atropine, phenylephrine, ephedrine, flurbiprofen axetil, sulbactam-ampicillin and indocyanine green were administered as required. The surgery ended uneventfully after a total of 387 minutes.

After confirmation of limb movement, sugammadex 200 mg (4 mg/kg) was injected to reverse residual neuromuscular blockade. Three minutes after sugammadex administration, the endotracheal tube was removed. Immediately following tracheal extubation, the arterial blood pressure (BP) decreased to 66/34 mmHg without a change in heart rate (70 /minute). No skin changes on the extremities or trunk were noted, but bilateral palpebral swellings were

Table 1
Results of the skin prick test

Solution	Wheal (mm)	Flare (mm)	Assessment
1. S+R undiluted	–	25 × 21	+
2. S+R 1:10-diluted	–	–	–
3. S+R 1:100-diluted	–	–	–
4. S+R 1:1000-diluted	–	–	–
5. S undiluted	5	29 × 20	+
6. S 1:10-diluted	–	24 × 17	+
7. S 1:100-diluted	–	6 × 6	–
8. S 1:1000-diluted	4	25 × 20	+
9. 0.9% saline	–	–	–
10. Histamine	5	34 × 30	+

The number for each solution is the same as that shown in Figure 1. Solutions were diluted in 0.9% saline. Wheal size is presented as the length of the long diameter, and flare size is presented as the long × short diameter. S+R=sugammadex-rocuronium mixture, S=sugammadex.

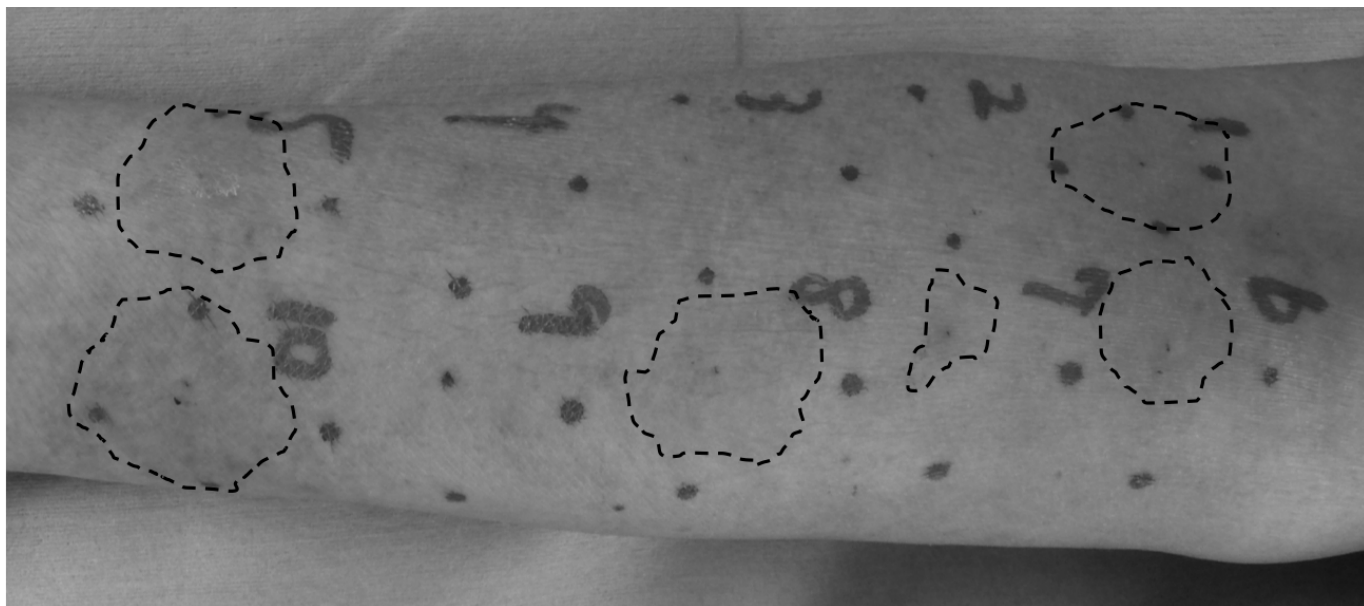


Figure 1: Evaluation of the skin prick test at 15 minutes. Broken lines show the extent of flares. Reaction of the skin prick test in each number is summarised in Table 1.

observed. Anaphylactic shock induced by sugammadex was suspected, because all other drugs had been administered at least 25 minutes earlier. Intravenous adrenaline 0.05 mg was administered and the BP increased to 91/47 mmHg. An infusion of adrenaline was initiated and haemodynamic stability was achieved, following which, the patient was transferred to our ICU. The patient had an uneventful postoperative course, except for mild gastric irritation. She was transferred to the ward on the following day and discharged on postoperative day 10.

On postoperative day 43, a skin prick test was performed using 0.9% saline (negative control), histamine 10 mg/ml (positive control), sugammadex 100 mg/ml (1:1000, 1:100, and 1:10, diluted in saline and undiluted), as well as previously mixed equal volumes of sugammadex 100 mg/ml and rocuronium 10 mg/ml (1:1000, 1:100, and 1:10, diluted in saline, and undiluted). Evaluation for skin reactions was conducted 15 minutes later. A positive reaction was defined as a wheal of diameter >3 mm, or a flare over twice the diameter of the negative control or >15 mm. Positive reactions were observed in response to three concentrations of sugammadex solutions (1:1000, 1:10, and undiluted) and to the undiluted sugammadex–rocuronium mixture solution (Table 1, Figure 1).

Suspected cases of sugammadex-induced anaphylaxis have been reported sporadically; however, the total number of previous reports remains small^{1–4}. In these reports, sugammadex-induced anaphylaxis appeared to be associated with a wide range of severities, and diagnostic protocols have yet to be established. Sugammadex binds to rocuronium, forming a sugammadex–rocuronium complex immediately after intravenous administration. Thus, it is important to determine whether anaphylaxis occurring immediately after sugammadex administration is due to free sugammadex or

the complex. Sadleir et al addressed this issue by performing intradermal skin tests with both sugammadex alone and sugammadex–rocuronium mixtures (1:3.6 molecular ratio) in two cases². Consequently, both patients demonstrated positive skin responses to sugammadex solutions. However, neither patient demonstrated positive skin responses to sugammadex–rocuronium mixture solutions. In our case, a skin prick test was performed using four different concentrations (1:1000, 1:100, 1:10, and undiluted) of sugammadex and of sugammadex–rocuronium mixtures. Positive reactions were observed in response to three different concentrations of sugammadex solutions (1:1000, 1:10, and undiluted) and the undiluted sugammadex–rocuronium mixture solution. Our results differ from those of Sadleir et al, because unlike their findings, we observed a positive reaction to undiluted sugammadex–rocuronium. However, we used a mixture of 100 mg sugammadex and 10 mg rocuronium, resulting in a 2.8:1 molecular ratio, whereas Sadleir et al used a ratio of 1:3.6. Accordingly, our mixtures had a larger amount of free sugammadex molecules, particularly in our undiluted sugammadex–rocuronium mixture solution, as sugammadex and rocuronium form a complex in a 1:1 molecular ratio. In contrast, very few free sugammadex molecules may have been present in the sugammadex–rocuronium mixture solutions used by Sadleir et al. Taken together, our results corroborate the conclusion of Sadleir et al that a positive skin reaction can be triggered by free sugammadex molecules.

We cannot explain the negative results observed with the 1:10 and 1:100 diluted sugammadex–rocuronium mixture solutions, because the number of free sugammadex molecules in these solutions must have been much greater than in the 1:1000 diluted sugammadex solution, which induced a positive skin reaction. We consider it unlikely

that both of these reactions were false negatives, because the positive and negative controls clearly demonstrated expected results. A possible explanation for the negative results is that the interaction between sugammadex and immunoglobulin E may be attenuated by sugammadex–rocuronium complexes. In any case, it would be a prudent clinical practice not to administer an excessive dose of sugammadex. If we had administered 100 mg sugammadex (2 mg/kg) instead of 200 mg, the anaphylactic reaction might have been attenuated.

In conclusion, we suggest that free sugammadex molecules can induce anaphylaxis, and the antigenicity of sugammadex may be decreased following binding to rocuronium. The avoidance of unnecessarily large doses of sugammadex may alleviate the severity of anaphylaxis, in those rare occasions in which it may occur.

T. Nakanishi

K. Ishida

K. Utada

M. Yamaguchi

M. Matsumoto

Yamaguchi, Japan

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Leptin levels and clinical outcomes in patients with systemic inflammatory response syndrome

Leptin is a hormone which helps to control weight and eating behaviour by activation of different hypothalamic receptors in response to food availability or shortage¹. Overall, it balances anabolic and catabolic hypothalamic activation in order to maintain adequate food intake and metabolic rate². It has been shown that leptin may have a role in the immune response to inflammatory stimuli. Studies in man have shown that, during sepsis and septic shock, leptin levels increase 2.3 and 4.2 fold, respectively, compared to controls, and that high leptin and low interleukin 6 (IL-6) levels are significantly associated with a reduced mortality³.

After obtaining hospital ethics approval (Approval No.: 36-23.03.07) and relevant trial registration (NCT00893932), the serial changes in leptin levels of 53 patients, admitted to the medical ICU with systemic inflammatory response syndrome over a ten-month period, were assessed. Pregnant patients or those younger than 18 years were excluded

from the study. Leptin, IL-6 and tumour necrosis factor alpha (TNF α) levels were measured (using ELISA: R&D kits) on admission and then three times a week up to 14 days unless they were discharged from the ICU or died. Patients' nutritional status and anthropometric measurements, including body mass index, body fat store (using a Jamar® Medical Skinfold Caliper, Patterson Medical, North Ryde, New South Wales) and daily caloric requirements, were assessed by the dietitian⁴. The overall clinical outcome of the patient during ICU stay was initially classified into three groups: improved, deteriorated or erratic (improved initially but subsequently deteriorated). Because of the small number of patients involved, patients who deteriorated or those who had an erratic course were pooled as a group when compared to those who improved after ICU admission. The overall clinical assessment of the study patients was performed by the primary investigator before the leptin levels were available to her.

Leptin, TNF α , and IL-6 levels were transformed by logarithm to improve the normality of their distribution. Continuous variables were compared using the Student's t-test or non-parametric Mann–Whitney U test. Categorical variables were compared using chi-square or Fisher's exact tests. Serial comparisons between groups were performed using the analysis of variance and Kruskal–Wallis analysis of variance. Time effect was analysed using the Greenhouse Geisser test. Correlations between continuous variables were performed using Pearson's correlation coefficient and Spearman's Rank correlation coefficient (R).

The mean age of the cohort was 63.5 (standard deviation [SD] $\pm$ 17.1) years and 55% were male. The mean Acute Physiology and Chronic Health Evaluation II score was 27.42 (SD $\pm$ 9.64) and admission C-reactive protein level was 1600 nmol/l (SD $\pm$ 1210). The most common admission diagnoses were sepsis (64%) and pneumonia (36%). A total of 18 (34%) patients completed the 14-day follow-up in this study, 21 and 14 patients were discharged or died earlier, respectively. The mean body mass index of the male and female patients were 24.5 kg/m² and 25.9 kg/m², respectively. The leptin levels appeared to be higher in the females (mean 27.72 $\pm$ 71.58 μ g/l) than the males (mean 12.63 $\pm$ 15.21 μ g/l), however this difference was not statistically significant ($P=0.95$). Leptin levels were positively correlated with weight, body fat store and body mass index ($R=0.39$, 0.38 and 0.42 respectively), but not caloric intake relative to daily requirements ($R=0.01$).

The associations between admission log leptin, TNF α , IL-6 and patients' subsequent clinical status are described in Table 1. Admission leptin levels were significantly higher among those who subsequently improved compared to those who deteriorated (mean 0.98 $\pm$ SD 0.59 versus mean 0.57 $\pm$ SD 0.63 μ g/l, respectively, $P=0.02$), and in those who died versus survivors. Conversely, IL-6 levels were significantly higher in those who deteriorated subsequently (mean 0.29 $\pm$ SD 0.11 IU/ml versus mean 0.21 $\pm$ SD 0.07 IU/ml, respectively, $P=0.002$) or died. There was no significant correlation between IL-6 and leptin levels ($R=-0.227$, $P=0.1$) or between

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