

In Response

Thank you for the opportunity to respond to the comments of Dr Nielsen¹ about our article.² Although we agree that patient satisfaction is an important topic, it is not routinely assessed in our hospital. We do know, anecdotally, of considerable numbers of patients who require serial procedures (eg, for colonoscopy) and who refuse to again have operator-provided sedation (using midazolam and fentanyl) after having experienced sedation administered in the manner described in our article. Nonetheless, we agree fully that data trump “comfortable” assumptions. This requires further prospective study using carefully thought-out methods. Patient satisfaction is a tricky construct, however, particularly if it is assessed after drugs with powerful amnesic effects were used. We have all seen patients undergoing sedation for a procedure who experience pain and discomfort and express their dissatisfaction, but later have no memory of it and express complete satisfaction with their sedation. Is “anguish unre-membered” acceptable or not? This issue raises challenges that are not only practical but also ethical and philosophical.

Finally, in response to the other points he raises, we offer the following information. It is certainly worth investigating his hypothesis of a relationship between operator experience and the occurrence of adverse events, but unfortunately, we cannot do this analysis ourselves, as we did not collect information concerning operator identity or experience in our database, which is based on anesthetic records of the procedures. The matter he raises about the use of high-flow nasal oxygen is highly topical and valid, but this technique was not used in our hospital during the study period (2014–2017).

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Intraoperative Anaphylaxis: Definition Determines Detection

To the Editor

We read with great interest the article by Burbridge¹ and accompanying editorial,² which report an incidence of anaphylaxis to sugammadex substantially lower than previously reported rates. While we agree with the author's analysis and conclusions, we caution readers to place these findings in appropriate context and keep in mind that case screening criteria can significantly bias estimates of incidence.

Timely and accurate diagnosis of anaphylaxis in the operating room is difficult. It is even more difficult to identify a causative agent.³ Objective measures are imperfect. For example, tryptase levels have high specificity, but low sensitivity and long turnaround times for determination.⁴ Hypotension may be noted immediately but is nonspecific in the operating room environment, especially with propofol inductions. Subjective and clinical assessments are similarly flawed. To highlight this point, in a study of 21 experienced anesthesiology teams taking part in a simulated anaphylactic shock scenario, none of the teams made the correct diagnosis after 10 minutes. Only 6 teams considered the diagnosis after prompting from an instructor, likely due to the nonspecificity of presenting signs and symptoms.⁵

Case screening criteria, which are often informed by these clinical signs and symptoms, can also skew estimates. In Burbridge,¹ cases had to have a sugammadex allergy listed in the medical record and/or coadministration of sugammadex and epinephrine within the same anesthesia record to be eligible for manual review and inclusion. Even with these broad criteria, cases of interest may be excluded. We note, for example, that the single patient who experienced anaphylaxis in Min et al⁶—the source of the markedly higher incidence estimate quoted in the sugammadex package insert—did not receive epinephrine, and would have been excluded from the Burbridge¹ study if sugammadex allergy was not written in the chart. Given the extremely low incidence of these events, selection biases causing inclusion or exclusion of even a single case could have a marked effect on the incidence estimate.

In light of the potential for detection and selection biases, methods for estimation of anaphylaxis incidence warrant careful consideration and standardization. In the absence of a reliable standard, care must be taken to interpret findings within the context of their respective methodologies.

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In Response

Clark et al¹ are thanked for their thoughtful reply. These authors argue that hypotension is common under general anesthesia, presumably to correctly call attention to hypotension treatment not being diagnostic of anaphylaxis. By designing the study to include charts in which epinephrine and sugammadex were coadministered, the objective was to include cases where epinephrine, which is first-line therapy for anaphylaxis, was administered. These charts underwent extensive review to confirm or exclude the diagnosis based on available objective and subjective clinical criteria and were judged according to the World Allergy Organization (WAO) criteria. However, the argument put forth by Clark et al¹ that hypotension is a nonspecific finding is an oversimplification. While hypotensive episodes are not unusual during anesthesia care, they require immediate and

swift evaluation to quickly and accurately diagnose and formulate a treatment plan, which in itself requires constant and ongoing evaluation. The cited simulation article, while interesting, should not be extrapolated to support the notion that a critical and life-threatening incident such as anaphylaxis is misdiagnosed in a majority of cases under the real world care of anesthesiologists.

These authors correctly raise the critical point of screening criteria as playing an essential role in calculating the incidence estimate. They cite the sole case of anaphylaxis in Min et al² as an example. This study utilized the Sampson criteria to diagnose and stratify each hypersensitivity reaction's severity in their study. All patients in this study were conscious and could communicate any subjective symptoms to a study physician. This case would have been challenging to detect under general anesthesia because many of the symptoms were elicited verbally from subjects, and was treated only with diphenhydramine and hydrocortisone. These authors acknowledge in their discussion that increased detection rates of hypersensitivity reactions may be due to studying conscious subjects because of the additional clinical information that can be gathered.

In contrast, the 2 patients who suffered anaphylactic reactions in Burbridge³ were under general anesthesia. Both patients suffered significant hypotensive episodes, among other symptoms, which were successfully treated with epinephrine. Notably, Clark et al¹ are incorrect that a patient who did not receive epinephrine would have been omitted in the study. Epinephrine coadministration was not required to be included for analysis because the other data search captured any patient with a sugammadex allergy listed in their chart. In this case, hypersensitivity reactions which did not require epinephrine could have been captured, however there were no such patients identified.

Differences in methodologies may produce different incidence estimates but mounting evidence suggests that sugammadex is much safer to administer than previously thought. Additional large-scale studies will undoubtedly shed more light on this subject.

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