Bleeding Risk in Surgical Patients Receiving Sugammadex: Definitive Conclusions Are Not Yet Possible

To the Editor:

I read with great interest the article by Rahe-Meyer *et al.*[1] evaluating the effect of sugammadex on postsurgical bleeding and coagulation tests in patients receiving thromboprophylaxis after major hip or knee surgery. It provides important evidence in support of the safety of sugammadex in reversing rocuronium (or vecuronium)-induced neuromuscular blockade.[1] However, there is one aspect of this study that deserves comment.

The authors estimated the relative risk (RR) and 95% CI of bleeding events to be 0.70 (0.38 to 1.29) for sugammadex *versus* usual care.[1] Four groups were considered for stratified analysis. The two largest were a group of 990 patients (84% of cases) treated with low-molecular-weight heparin and a group of 144 patients (12% of cases) treated with antiplatelet plus anticoagulant drugs.[1]

Davidson *et al.*[2] recently demonstrated that by inhibiting platelet aggregation, aspirin and other nonsteroidal antiinflammatory drugs increase the risk of bleeding in patients receiving anticoagulant therapy to prevent recurrent venous thromboembolism.[2] In their study, the hazard ratios, adjusted for sex, age, and creatinine clearance, were 1.59 (95% CI, 1.17 to 2.17) for clinically relevant bleeding and 1.50 (95% CI, 0.74 to 3.05) for major bleeding during concomitant aspirin–anticoagulant treatment and 1.65 (95% CI, 1.26 to 2.17) for clinically relevant bleeding and 2.28 (95% CI, 1.28 to 4.04) for major bleeding during concomitant nonsteroidal antiinflammatory drug–anticoagulant treatment.

Although sugammadex was not associated with an increased risk of bleeding in the study by Rahe-Meyer *et al.*,[1] no data are presented regarding the potential difference in RR (95% CI) of bleeding events for the anticoagulant therapy (such as with low-molecular-weight heparin, unfractionated heparin, or vitamin K antagonists) *versus* antiplatelet–anticoagulant treatment groups. Considering the results of the study by Davidson *et al.*,[2] it is possible that the RR (95% CI) for sugammadex *versus* usual care may be higher in patients receiving antiplatelet–anticoagulant therapy than in those receiving anticoagulant therapy. As the results of the previous reports by Rahe-Meyer *et al.*[1] confirmed in surgical patients that sugammadex produces minor and transient (<1 h) prolongation of the activated partial thromboplastin time and prothrombin time (international normalized ratio),[3] the question arises whether sugammadex has the potential to increase the risk of early postoperative bleeding in a larger group of patients receiving concomitant antiplatelet–anticoagulant treatment. Considering the results of Rahe-Meyer *et al.*[1] and previous studies,[3–5] it appears unlikely that sugammadex administered at the end of a surgical procedure will cause clinically significant bleeding.[6] Additional data, however, are necessary to definitively conclude that sugammadex does not produce clinically important postoperative bleeding, even in patients receiving concomitant antiplatelet–anticoagulant therapy.

Competing Interests

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In Reply:

Dr. Carron raises the question that patients receiving thromboprophylaxis with low molecular weight heparins (LMWH) and antiplatelet drugs acetylsalicylic acid (ASA) might have an increased bleeding risk if exposed to sugammadex. He referred to the study by Davidson *et al.*[1] that showed an increased bleeding risk for the combination of antithrombotic and antiplatelet drugs. In contrast to the

study discussed here, Davidson's study was assessing a nonsurgical scenario in which therapeutic doses of oral anticoagulants instead of prophylactic LMWHs were used.

In our trial, roughly 12% of the study population of 1,184 patients, or 144 patients (73 randomized to sugammadex and 71 randomized to usual care), were treated with concomitant LMWH and ASA. There were very few bleeding events in this subgroup, with only four among those that received sugammadex and two in those that received usual care; these numbers are too low to allow for a meaningful comparison of bleeding rates in patients treated with sugammadex *versus* those treated with usual care. Very few patients were treated with concomitant ASA only (n = 29 total, including 15 in the sugammadex group and 14 in the usual care group); of those patients on ASA only, there were no bleeding events in either the sugammadex or the usual care groups.

Of note, the addition of ASA to LMWH did not increase the bleeding risk among patients who received usual care (4.3% bleeding rate in patients on LMWH compared with 2.8% in patients on LMWH plus ASA who received usual care). Thus, the overall bleeding risk is low in patients receiving LMWH that are randomized to either sugammadex or usual care, and despite the limited experience in this study, it appears that the addition of ASA likely does not confer additional bleeding risk compared with that seen with background LMWH treatment.

As a result, the data of this trial give no reason to interrupt required treatment with ASA in a similar clinical scenario.

Competing Interests

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Incidence of Intraoperative Hypersensitivity Reactions: What's This About?

To the Editor:

Saager *et al.*[1] used a methodology combining electronic search strategies and clinical adjudication to retrospectively determine the incidence of intraoperative hypersensitivity events in one U.S. surgical center. The authors concluded that the overall incidence of anaphylaxis was 1 in 4,583 surgeries, whereas that of hypersensitivity was 1 in 677. However, major methodologic issues should be highlighted, and the results must be debated because no conclusion can be effectively drawn from this study.

First, the claim that "the overall incidence of anaphylaxis was similar to that reported in previous studies but that of hypersensitivity reactions was nearly seven times higher"[1] is not accurate because this has not been proved. In addition, it is supposed that hypersensitivity was used to designate immediate hypersensitivity because delayed hypersensitivity does not arise during the perioperative period. Thus, six types of criteria were arbitrarily selected to identify potential perioperative hypersensitivity in 178,746 surgeries during the 7-yr study period. The adjudication committee further selected 264 cases of immediate hypersensitivity corresponding to 7% of the study population by 1, 2, 3, or 4 search criteria and subsequently classified these cases according to a modified Ring and Messmer scale. The search criteria included clinical features, biologic measurements, *e.g.*, histamine, tryptase, or IgE (total or specific), and selected preferred terms. Some of these latter should not have been used because they are not consistent with immediate hypersensitivity. Particularly, the first-use syndrome has been described during hemodialysis[2]; fixed eruption and drug dermatitis belong to cell-mediated hypersensitivity that has a delayed presentation[3]; and flushing, sensation of foreign body, and laryngospasm or stridor do not belong to perioperative immediate hypersensitivity *per se*.[4] Therefore, it is unclear whether only clinical features related to perioperative immediate hypersensitivity[4] were considered for including the 264 cases. In addition, the timing between the introduction of the suspected trigger and the onset of clinical features is lacking. Accordingly, the onset delay is a useful argument in the diagnostic approach of perioperative immediate hypersensitivity, which usually occurs within minutes, even 1 min, of anesthetic induction.[4]

Second, laboratory tests were performed in only five patients (1.7%) but unfortunately remained undetailed. One should keep in mind that tryptase increase is highly suggestive of mast cell activation as seen in anaphylaxis.[4–7] In contrast, total IgE has no indication in the diagnostic approach of perioperative immediate hypersensitivity,[7] whereas the identification of serum IgE to quaternary ammonium provides possible evidence of IgE sensitization but does not prove that a neuromuscular-blocking agent elicited the immediate reaction *per se*.[4,6,8]

Third, skin testing was not performed, and thus, none of these 264 cases can be considered to be definitively supported by an appropriate allergologic assessment. The analysis of biologic and skin tests results should always be tied to