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Propofol and Additives: Please Consider Zebras Besides Horses When You Hear Hooves

To the Editor:

We read with great interest the article by Schilling *et al.* dealing with effects of sevoflurane and desflurane as volatile anesthetics compared with propofol as an intravenous anesthetic and the relationship between pulmonary and systemic inflammation in patients undergoing open thoracic surgery.[1] Authors remarked that proinflammatory cytokines increased in the ventilated lung after one lung ventilation. Mediator release was more enhanced during propofol anesthesia compared with desflurane or sevoflurane administration. Postoperatively, the proinflammatory cytokines tumor necrosis factor- α ($P < 0.001$), interleukin-1β (IL-1β) ($P < 0.002$), and interleukin 8 (IL-8) ($P < 0.025$) were more increased in patients during propofol administration compared with both volatile anesthesia groups, and postoperative serum concentration of IL-6 was increased in all patient groups after thoracic surgery ($P < 0.001$). The authors concluded that one-lung ventilation increases the alveolar concentrations of proinflammatory mediators in the ventilated lung. Both desflurane and sevoflurane suppress the local alveolar, but not the systemic, inflammatory responses to one-lung ventilation and thoracic surgery.

Lung injury after thoracic surgery is a relatively uncommon but major complication with high mortality. Many factors, including cytokine imbalance, ischemia reperfusion injury, and the use of one-lung ventilation, are involved in this process apart from the surgical insult itself.[2] In our opinion, a point of this work is not sufficiently clear. EDTA and sulfite might be added as antimicrobial agents to several formulations of propofol, which may have different physiologic responses. Herr *et al.*[3] showed that the patients in the surgical intensive care unit receiving propofol with EDTA had significantly reduced mortality rates at 7 and 28 days compared with those receiving propofol without EDTA. Haitsma *et al.*[4] compared the effects of propofol with EDTA, propofol with sulfite, and ketamine/midazolam on tumor necrosis factor- α, interleukin-6 (IL-6), and macrophage inflammatory protein-2 in an animal study. They showed that bronchoalveolar lavage IL-6 was significantly higher in the propofol with sulfite group compared with both the ketamine/midazolam and the propofol with EDTA groups. They also remarked that pulmonary IL-6 can be modulated by additives in systemic anesthesia.

Accordingly, we think that reporting detailed formula of propofol in studies evaluating the effect of propofol on inflammatory responses would be crucial, and we hope that the previously mentioned comments might add to the value of the manuscript by Schilling *et al.*[1]

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In Reply:

We appreciate the great interest of Dr. Yalcin and Dr. Aydogan in reading our article,[1] and we would like to thank them for their important comment regarding the different physiologic responses of propofol and its additives. Propofol has become one of the most widely administered drugs for induction and maintenance of anesthesia and for sedation in the intensive care unit. Therefore, we have chosen this substance as well to provide standardized total intravenous anesthesia in the control group of our clinical study. In patients who received total intravenous anesthesia with propofol, release of proinflammatory cytokines into the alveoli of the ventilated lung was more increased after one-lung ventilation and open thoracic surgery, in comparison with the administration of desflurane or sevoflurane in other patient groups. The time course of pulmonary cytokine release confirms previous clinical studies, which demonstrate an enhanced mediator expression during propofol anesthesia for thoracic surgery.[2,3]

However, highly lipid-soluble drugs such as propofol may also affect the inflammatory response. Propofol decreases granulocyte recruitment and neutrophil activation by reduction of polarization, chemotaxis, and inhibition of the respiratory burst in clinically used concentrations.[4] In addition, it exerts antioxidative properties, which may prevent the organism from oxidative stress.[5] The pronounced proinflammatory response should therefore not be interpreted as being

increased by propofol administration in our study. This immune reaction was unquestionably diminished as well but to a lesser extent.[6]

Moreover, the additives EDTA and sodium metabisulfite are biologically active and are used to retard bacterial contamination in propofol formulations. Whereas sulfite supports lipid peroxidation in propofol emulsions[7] and increases proinflammatory interleukin-6 release in lipopolysaccharide-injured rat lungs,[8] antiinflammatory properties of EDTA may have beneficial effects in patients with sepsis and systemic inflammatory response syndrome. Accordingly, surgical intensive care unit patients who received propofol with EDTA had significantly reduced mortality rates in comparison with those who received propofol without EDTA.[9] In contrast, clinical variables and incidence of adverse events were not affected by propofol/EDTA in patients after cardiac surgery.[10]

The administration of propofol formulations with EDTA or sodium metabisulfite may thus increase the variability of the inflammatory response. For that reason, we used a single propofol formulation without EDTA or sulfite (Propofol-Lipuro 20 mg/ml, B. Braun Melsungen, Melsungen, Germany) in our study.[1] This preparation contains refined soybean oil, medium-chain triglycerides, glycerol, egg lecithin, and sodium oleate.

In conclusion, it is essential to take the immunomodulatory properties of different anesthetic drugs and their potential additives into account to avoid misinterpretation of clinical reports. However, the amount of reliable data on inflammatory effects of additive drugs is limited and often conflicting; therefore, more experimental and clinical studies are needed.

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There Is Lack of Evidence that Succinylcholine Should Be Avoided in Patients on Statin Therapy

To the Editor:

I read with great concern the recent editorial from Dr. Lee, the title of which provided a very strong message to the readers of ANESTHESIOLOGY: "Succinylcholine Should Be Avoided in Patients on Statin Therapy."[1] The editorial was in reference to the article by Turan *et al.* from the Department of Outcomes Research at the Anesthesiology Institute at Cleveland Clinic in Cleveland, Ohio.[2] The Cleveland Clinic authors performed a well designed study and were correct when they concluded that despite statistically significant results, the difference on plasma myoglobin concentration attributed to the use of succinylcholine in patients taking statins was likely to be small and probably of limited clinical consequences.

Lee based the strong and conclusive title of his editorial on a hypothesis that the negative finding of Turan *et al.*'s study was probably due to the fact that subjects at high risk for the development of high myoglobin plasma concentrations were excluded from the protocol, and that the inclusion of those subjects would have led to different results. He specifically mentioned the elderly population as a particularly vulnerable group because of its limited functional reserve. Although only another well designed study will be able to answer this question, I hypothesize that, if pursued, the study will find similar results as the one found by Turan *et al.* Elderly pa-

These letters were sent to the author of the above-referenced article (by Turan *et al.*), who declined to reply. Only the author of the editorial (by Lee) replied.—James C. Eisenach, M.D., Editor-in-Chief.