Competing Interests

Many of the authors are unpaid volunteers for the nonprofit Malignant Hyperthermia Association of the United States (MHAUS; Sherburne, New York). They have served variously as directors of The North American Malignant Hyperthermia Registry of MHAUS and members of the board of MHAUS, the Professional Advisory Council of MHAUS, and/or the Malignant Hyperthermia Hotline of MHAUS. All of these positions are voluntary and unpaid. Many participated in the drafting of the current MHAUS recommendation for dantrolene availability in anesthetizing locations. Many of the authors have traveled to malignant hyperthermia conferences in the United States or Canada with MHAUS financial support. MHAUS receives funding support from MHAUS members, customers, medical associations and societies, foundations, and various corporations, including Eagle Pharmaceuticals (Woodcliff Lake, New Jersey), PAR Pharmaceuticals (Chestnut Ridge, New York), and U.S. WorldMeds, LLC (Louisville, Kentucky). Dr. Belani received several vials of Ryanodex from Eagle Pharmaceuticals, Inc., for use in a research study. Dr. Mashman has received a grant from Eagle Pharmaceuticals, Inc., for three vials of Ryanodex to bring on a medical mission trip. Dr. Riazi has received a consulting fee from Norgine Pharmaceuticals (Amsterdam, The Netherlands) and is also a member of the scientific advisory board of the RYR1 Foundation (Pittsburgh, Pennsylvania). Dr. Sivak has been a principal investigator for a Merck (Kenilworth, New Jersey) sponsored study of sugammadex (November 7, 2017 through August 3, 2018).

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Opioid-induced Ventilatory Depression in Sleep Apnea: Comment

To the Editor:

On the front page of the February 2019 issue of Anesthesiology, the article by Doufas *et al.* was encapsulated as, "Adults with Obstructive Sleep Apnea Do Not Have Increased Sensitivity to Opioid-induced Ventilatory Depression."[1] This is potentially misleading.

The complexity of the study design, pharmacokinetic/pharmacodynamic modeling, and the assumptions and limitations of the study may be beyond the understanding of the average reader. In their accompanying editorial, Henthorn and Olofsen did an admirable job explaining the many limitations.[2] They stated, "...we should be very cautious drawing conclusions in the language of pharmacokinetics–pharmacodynamics when there are no drug concentrations (pharmacokinetics) data and when there is non–steady-state effect data and either the onset effect or offset effect is missing."

The front page title, however, suggests the study endpoint of Doufas *et al.* can be broadly interpreted as applicable to all opioids in all clinical situations encountered by obstructive sleep apnea patients, which is overly simplistic. Is a target-controlled infusion of 4 ng/ml of remifentanil for 10 min in a well-lit and noisy operating room in a patient anticipating surgery an appropriate surrogate for the level of consciousness, airway, and respiratory dynamics of patients with obstructive sleep apnea on morphine patient-controlled analgesia in a quiet hospital ward at nighttime? Even

the study authors acknowledge this in their "Discussion" section: "...our findings pertain to awake patients with obstructive sleep apnea and exercise caution when opioids are administered to patients with decreased state of arousal."

Cases of patients with moderate to severe sleep apnea suffering fatal opioid-induced ventilatory depression postoperatively are increasingly reported, and the evidence of worse outcomes in this cohort is undisputed.[3–5] Additionally, the occurrence of apneic events in postoperative patients on opioids is a consistent finding in both retrospective and prospective cohort studies.[6] More than 10 yr of work by the Anesthesia Patient Safety Foundation (Rochester, Minnesota), Society for Anesthesia and Sleep Medicine (Milwaukee, Wisconsin), American Society of Anesthesiologists (Schaumburg, Illinois), Institute of Safe Medication Practices (Horsham, Pennsylvania), and others to advocate guidelines for safer parenteral opioid use in these patients are finally bearing fruit. Yet the reluctance to adopt these guidelines by skeptics may be emboldened by cursory attention to the title of this edition of the Journal. We sincerely hope the editors can rectify this potential for confusion, which is critical to the safety of these patients.

Competing Interests

Dr. Overdyk received consulting fees from Medtronic (Dublin, Ireland). Dr. Dahan has received speaker and consultancy fees from Grunenthal (Aachen, Germany), Medasense (Ramat Gan, Israel), MSD (Kenilworth, New Jersey), and Philips (Eindhoven, The Netherlands). His research unit received grants from Medasense, Bedrocan (Veendam, The Netherlands), and MSD. Dr. Chung received research support from the Ontario Ministry of Health and Long-Term Care (Toronto, Canada), University Health Network Foundation (Toronto, Canada), Medtronics grants to the institution, Up-to-Date royalties, and STOP-Bang proprietary to the University Health Network. Dr. Warner is president of the Anesthesia Patient Safety Foundation (Rochester, Minnesota).

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Opioid-induced Ventilatory Depression in Sleep Apnea: Reply

In Reply:

Our recent article on remifentanil in patients with obstructive sleep apnea concluded that "Obstructive sleep apnea status, apnea/hypopnea events per hour of sleep, or minimum nocturnal oxygen saturation measured by pulse oximetry did not influence the sensitivity to remifentanil-induced ventilatory depression in awake patients receiving a remifentanil infusion of 0.2 $\mu g \cdot kg^{-1}$ of ideal body weight per minute."[1] Our conclusion is supported by directly observed ventilation during remifentanil infusion, analyzed using published and validated models of remifentanil pharmacokinetics and the pharmacodynamic interaction between remifentanil and carbon dioxide on ventilation, and, as highlighted by the Editorial View by Henthorn and

Olofsen,[2] multiple analyses found that the absence of plasma concentration data did not significantly affect the estimate for the interindividual variability of the effect site concentration of remifentanil at which half-maximal ventilatory depression was observed, so it is unlikely our conclusion was affected. We agree with Overdyk *et al.* that our findings should not be extrapolated to other clinical scenarios where patients with obstructive sleep apnea may be at increased risk of opioid-induced ventilatory depression.

Competing Interests

The authors declare no competing interests.

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Chlorhexidine Inefficacy in Ventilated Patients: Comment

To the Editor:

The recent article by La Combe *et al.* is timely, directly challenging the practice of using oral chlorhexidine in intubated patients to reduce oral bacterial counts and ventilator-associated pneumonia.[1] While documenting a lack of efficacy of chlorhexidine to reduce bacterial load in the oropharynx, they failed to address the specific known pulmonary toxicity of chlorhexidine or evaluate the direct toxic impact of chlorhexidine "silent aspiration" into the lung, leaking between endotracheal tube cuff and tracheal mucosa. This would have been of great interest, as specific toxicology concerns remain discounted and with their administration of the 15-ml volumes and 0.12% concentrations applied. The authors did indicate some studies that specifically linked oral chlorhexidine use to increased mortality.

I previously published concerns regarding the silent aspiration of chlorhexidine and toothpaste used in clinical ventilator-associated pneumonia bundles, when my wife nearly succumbed to "silent aspiration" pneumonia in 2015. Ventilator-associated pneumonia and aspiration pneumonia occurred only after a motor vehicle trauma with immediate intubation after 24 to 48 h of normal pulmonary and radiological findings.[2] Progressive and severe aspiration pneumonia then developed postoperatively and in conjunction with the prevailing ventilator-associated pneumonia bundle (chlorhexidine and toothpaste), until tracheostomy performed on the ninth day of intubation led to improvement, as secretions now exited onto the anterior neck above the cuff, instead of draining into the lungs.

I was astonished to find during my review of the literature that in animal studies, chlorhexidine greater than 0.1% concentrations exhibit significant pulmonary toxicity.[3,4] However, toxicity has not been specifically addressed in intubated humans, where "silent" pulmonary aspiration is a recognized and expected risk. Toothpaste (inorganic silicates) is also a particulate material used in ventilator-associated pneumonia with known pulmonary implications and should be similarly concerning, as well as the scandal involving chlorhexidine and the National Quality Forum's (Washington, DC) guidelines for sterile skin prep: The U.S. Justice Department settled a $40 million whistleblower lawsuit in early 2014, alleging that CareFusion (USA), the maker of ChloraPrep, had inappropriately influenced the National Quality Forum.[5] Thus, business interests and guidelines do not ensure patient safety. Both toothpaste and chlorhexidine have found support as ventilator-associated pneumonia bundle quality parameters to a large degree, because of dental hygiene use in nonintubated daily living care—without concerns specific to pulmonary dangers from laryngeal incompetence and silent aspiration, a problem known to be inherent in intubated patients.

Minimization of ventilator-associated pneumonia in 2019 may require specific investigations regarding "silent aspiration" as causative and the importance of (1) elimination of all pulmonary toxins introduced into the oral cavity, (2) maximally effective oral hygiene using pulmonary tolerated aqueous and antibiotic solutions *via* electrical power brushing,[6] and (3) early tracheostomy to allow egress of secretions from above the cuff and return of glottic protective closure mechanisms, where indicated.