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Will Xenon Be a Valuable Addition in Perioperative and Critical Care Settings?

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When the first clinical report of xenon's use as a general anesthetic appeared in the middle of the last century,[1] it seemed almost too good to be true. Surely, a compound that possesses many of the properties of an ideal anesthetic (stable, nonbiotransformable, nontoxic, nonflammable, nonirritant, low blood–gas partition coefficient) would be widely and quickly adopted into clinical practice. Why has this not happened? Among the factors that may have contributed to its sporadic use include xenon's high cost (predicated by the complex purification process of an exceedingly scarce element from the atmosphere), the need for a specialized delivery and monitoring system, the relatively recent (in the last decade) authorization from a regulatory agency for its marketing as a general anesthetic, and the "weirdness" of why a chemically inert compound can exert such powerful behavioral effects. Work from each of Bart Westerkamp (for the delivery system[2]), Air Liquide Sante (for the market authorization), and Nick Franks (for the explanation of how xenon can work as an anesthetic[3]) has sought to overcome the obstacles to xenon's broader appeal for general anesthesia. Notwithstanding these developments, xenon's widespread adoption is unlikely to occur without a convincing demonstration of the superiority of xenon's properties as a general anesthetic versus best of breed.

In this issue of *Anesthesia & Analgesia*, a group headed by Dr. T. J. Gan has used meta-analysis to aggregate the evidence from previous studies comparing xenon with both potent volatile anesthetics and the IV anesthetic propofol.[4] This commentary is designed to address how this new piece of evidence helps to appraise the benefit of xenon as a general anesthetic and to provide some observations as to the future utility of xenon in perioperative and critical care settings.[4]

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Before the publication of this meta-analysis, the largest comparative effectiveness study involved a 224-patient multicenter[6] clinical trial that reported on clinical outcomes (hemodynamics, respiratory parameters, and recovery) of xenon versus isoflurane as a general anesthetic for American Society of Anesthesiologists I to III surgical patients undergoing a relatively short procedure (<2 hours). Hence, by pooling together the results from 42 previous studies (see Table 1 in the study by Law et al.[4]) involving >2300 surgical patients, Law et al.'s meta-analysis substantially enhanced the power to study an effect of interest that extends beyond the primary outcomes in the initial studies.[4] The authors describe the intraoperative hemodynamic parameters to be relatively more stable with xenon versus that produced during anesthesia with either volatile anesthetics or propofol. The authors define a clinically significant change as one in which there is a difference of >20% (in either direction) from the baseline (preinduction value); this occurred in the case of xenon for heart rate, and this decline in heart rate exceeded that seen for either volatile agents (Figs. 2 and 4 in the study by Law et al.[4]) or propofol (Figs. 6 and 8), yet blood pressure is better maintained by xenon versus either volatile agents (Figs. 3 and 5) or propofol (Figs. 7 and 9). Additional results and hemodynamic parameters would be needed to determine which profile is, in turn, associated with better organ perfusion and meaningful clinical improvement. Regarding recovery (Figs. 10 and 11), the authors have confirmed the remarkable rapidity with which patients emerge from xenon anesthesia compared with even propofol. This context-insensitive feature of xenon has been attributed to its exceedingly low-solubility coefficients and to the fact that xenon has no metabolites, active or inactive, under biologic conditions.[5] However, these statistically significant results may lack clinical relevance because faster waking up and extubation did not result in a reduction in the length of stays in the postanesthesia care unit, the intensive care unit, and the hospital. This probably speaks to the diluting out of xenon's potential beneficial reanimation properties by other factors, especially bed management. Xenon was associated with a higher risk for postoperative nausea and vomiting (PONV; Fig. 12). In addition, it is interesting to note that this adverse event was not significantly more frequent in a direct comparison of xenon versus propofol, a validated antidote to PONV.[6] More notably, the very wide confidence intervals for the comparison of PONV with xenon versus propofol

strongly suggest that more data are necessary to conclude with confidence on the benefit of one agent compared with another.

Besides the merits of meta-analyses on enhancing statistical power and capturing effects closer to real-world clinical practices, such study design does carry some limitations (such as publication bias, selection bias, and heterogeneity between studies) that need to be addressed to bolster the validity of the conclusions. Specifically, in the case of Law et al.'s meta-analysis, the risk of "selection bias" is substantial. Gan's group has taken the customary approach of interrogating only those randomized controlled trials (RCTs) that are published in English potentially overlooking important findings reported in the non-English medical literature. For example, Russian investigators, with ready access to supplies of xenon purportedly stockpiled as a rocket propellant during the "Cold War" era, have been quite prolific in reporting in the Russian literature on the clinical effectiveness of xenon in a variety of surgical patients for neurosurgical, dental, and pediatric procedures, among others. Another selection bias relates to criteria that distinguish only the high-quality RCTs for analysis (e.g., inclusion/exclusion criteria, methods of randomization and blinding, dropouts, analyses); in the case of this meta-analysis, 123 RCTs have been reduced to 43 (Fig. 1). Apart from the elimination of 2 retracted publications, the other 78 studies were not further considered although they may contain relevant information. Additional sensitivity analyses including RCTs identified as potential sources of bias would be helpful to appreciate its impact on the results.

Our overarching question remains in what circumstances, and for whom, will clinicians use xenon for general anesthesia? Based on our interpretation of these meta-analytical data, it will be useful to explore how a clinical benefit can be derived from the use of a general anesthetic that consistently decreases heart rate while maintaining blood pressure and cardiac index. Therefore, it is gratifying to know that a noninferiority study of xenon versus sevoflurane anesthesia for noncardiac surgical patients with coronary artery disease has been undertaken (CARVASAXe trial; NCT01120405; EudraCT #2010-018703-28); the primary endpoint in that multicenter (all in France) 600-patient trial was myocardial necrosis within the first 3 postoperative days. Although the results have yet to undergo peer review, from the NCT website (https://clinicaltrials.gov/ct2/show/results/NCT01120405?term=xenon+and+cardiac&rank=4&sect=X301256#evnt; accessed May 30, 2015), it does appear that xenon anesthesia in this patient population was noninferior for their primary endpoint of myocardial necrosis; alas, the industry-sponsored CARVASAXe was not designed to test xenon's superiority.

Law et al.'s meta-analysis, together with the recently completed CARVASAXe trial, have thrown into sharp focus, where, if not for cardiovascular-compromised patients, will xenon general anesthesia be more valuable; given that xenon will always be more expensive than potent volatile and IV anesthetic agents, even those that are proprietary, a higher quality clinical outcome will need to be demonstrated. The search for the value of xenon general anesthesia needs another direction to convince the uncommitted who are not passionate about closed-circuit anesthetic gas delivery.

Although there are no clinical data to direct the search for a higher quality outcome after general anesthesia, there are at least three preclinical studies that suggest that xenon may ameliorate the neurotoxicity of volatile anesthetics in the developing brain.[7–9] Before clinical trials can be launched to address the potentially beneficial role of xenon for anesthetic-induced developmental neurotoxicity, studies in nonhuman primates need to be undertaken as advocated by a collaborative under the auspices of SmartTots[10]; currently, these are being pursued. In the adult anesthetic setting, an ongoing clinical study exploring the safety and efficacy of xenon in preventing delirium after surgical repair of patients with hip fractures will report soon.[11]

Critical care settings for which xenon may be appropriate include acute neurologic injuries in which pathophysiologic mechanisms that propagate ongoing damage are amenable to blockade by xenon; these pathophysiologic pathways include *N*-methyl-D-aspartate-induced excitotoxicity,[12] spreading depolarization,[13] and neuroapoptosis,[14] each of which can be attenuated by xenon. Neurologic injuries that invoke these mechanisms include ischemic–reperfusion injury after successful resuscitation from cardiac arrest ("postcardiac arrest syndrome"[15]), stroke, traumatic brain injury, and neonatal asphyxia ("hypoxia-induced encephalopathy"); in preclinical models, xenon has been shown to be efficacious in each of these acute neurologic injuries.[16–19] Preliminary results of clinical trials investigating xenon's efficacy in limiting ongoing injury in postcardiac arrest syndrome have reported on the feasibility and safety of delivering xenon to these critically ill patients[20]; a recently completed phase II clinical trial exploring xenon's efficacy in this setting will report soon. A preliminary clinical report on the use of xenon for hypoxia-induced encephalopathy revealed fewer convulsions, a clinical complication that is known to have an adverse effect on outcome.[21]

Xenon has also been explored in other ischemic–reperfusion injury settings because of its remarkable property of increasing the translational efficiency of hypoxia-inducible factor 1-α even under normoxic conditions.[22] Results from a preliminary clinical study confirm that erythropoietin level, a downstream marker of hypoxia-inducible factor 1-α activation with broad cytoprotective properties, is increased when xenon anesthesia versus sevoflurane anesthesia is used during coronary artery bypass graft surgery.[23] In a series of elegant preclinical transplantation models, Ma's group has reported that xenon improves the function of transplanted kidneys and limits the immunologic damage to other organs after a renal allograft.[24–28]

Because the current outcomes for anesthetic-induced developmental toxicity, acute neurologic injury, and transplantation of relatively ischemic organs may be either severely disabling or life-threatening, these are conditions for which the relatively high cost of xenon and its technically

demanding delivery devices become acceptable. Definitive clinical trials to exploit some of these indications are now being launched.

Law et al.'s[4] meta-analysis on the comparative effectiveness of xenon is a timely reminder that there remains unfinished business in defining under which circumstances, and for whom, this costly element makes clinical and economic sense. Clinical trials that address in which perioperative and critical care settings xenon is likely to be of benefit are being undertaken. The results of these trials will answer whether xenon has a bright future in the practice of anesthesiology and critical care as was first envisaged by Cullen and Gross[1] 65 years ago.

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