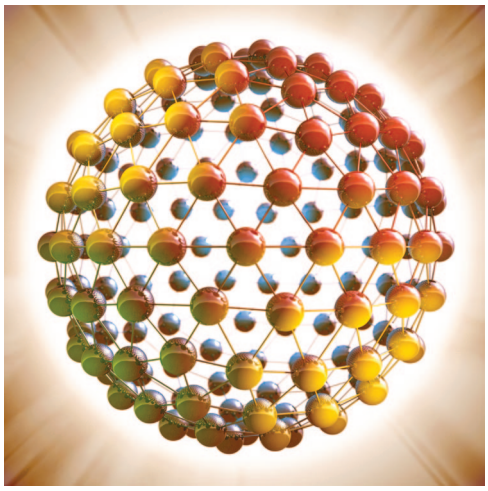
Getting Oil and Water to Mix

IV administration of halogenated and nonhalogenated ether and nonether alkane ("volatile") anesthetics has been explored for more than a century.[1] Of note, the earliest evaluations were in humans.[2–6] One immediate and significant challenge was formulation. Early endeavors simply dissolved the anesthetics in aqueous solutions, but low solubility and side effects were problematic. A variety of oil-in-water emulsions were tried, with the first successes described 50 yr ago.[2] In the current issue of ANESTHESIOLOGY, Jee *et al.* describe a novel "fat-free" approach to formulating a volatile anesthetic (sevoflurane) emulsion, and the IV anesthetic delivery which it enabled.[7]

Volatile anesthetics formulated as emulsions in Intralipid® (Fresenius Kabi AB, Uppsala, Sweden) or other fats have been shown to produce general anesthesia. Anesthesia could be induced with an emulsion, and once achieved, maintained by continuous infusion or by rebreathing.[2–6,8,9] Not surprisingly, induction time was shorter with IV compared with inhaled volatile anesthetics.[9,10] The minimum alveolar concentration of emulsified volatile anesthetics was significantly lower than that of inhaled anesthetics, attributed in part to effects of the IV lipid load on the blood:gas partition coefficient, but measured blood concentrations were equivalent.[9,10] Recovery time after emulsified volatile anesthetics was also rapid,[10,11] and emulsion formulation was reported to not affect the time course of isoflurane washout.[10]

Volatile anesthetic emulsions have also been shown to elicit other, more "nontraditional" effects caused by inhaled volatile anesthetics. Emulsified isoflurane and sevoflurane in anesthetic and subanesthetic concentrations were cardioprotective against reperfusuion injury when administered intravenously[12–15] or in cardioplegia solution.[16] Volatile anesthetics, encapsulated in lecithin microdroplets and injected intradermally, produced long-duration local anesthesia lasting several days in humans.[17,18] Volatile anesthetic emulsions have also been reported to produce epidural anesthesia in rabbits,[19] reversible conduction block in toad sciatic nerve,[20] and IV regional anesthesia in rats.[21]



"This new emulsion formulation of sevoflurane should facilitate additional investigations evaluating IV volatile anesthetic pharmacology, and the potential clinical application and utility of such a formulation."

Nevertheless, as summarized in this issue's ANESTHESIOLOGY article by the research team from the Departments of Anesthesiology and Chemistry and School of Pharmacy at the University of Wisconsin, volatile anesthetic emulsions formulated in Intralipid® or other fats have been limited by solubility, carrying capacity, and stability. In a previously reported effort to improve the amount of sevoflurane stably emulsified, the Wisconsin team created a copolymer (designated F13M5)-based surfactant nanoemulsion that could dissolve up to 20% sevoflurane by volume.[22] The sevoflurane emulsion, when injected intavenously, induced general anesthesia in rats and dogs with rapid onset and recovery.[22,23] However, the F13M5-based sevoflurane emulsion was accompanied by significant hypotension in the dogs, because of histamine release.[23] Moreover, in additional studies reported in this issue of ANESTHESIOLOGY, long-term stability testing of the original F13M5-based emulsion showed it to be unstable, leading to nanoparticle aggregation and formation of unacceptably large particles. The histamine release and formulation stability were significant safety issues necessitating a new formulation approach.

The investigators now report the successful formulation of sevoflurane with a newly developed polymer, forming a nanoemulsion containing 20% sevoflurane by volume.[7] The new emulsion was stable for more than 1 yr when stored at 4°C, and, when injected intravenously, produced general anesthesia in rats with rapid onset and recovery.

This new emulsion formulation of sevoflurane should facilitate additional investigations evaluating IV volatile anes-

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◆ This Editorial View accompanies the following article: Jee J-P, Parlato MC, Perkins MG, Mecozzi S, Pearce RA: Exceptionally stable fluorous emulsions for the intravenous delivery of volatile general anesthetics. ANESTHESIOLOGY 2012; 116:580–5.

thetic pharmacology, and the potential clinical application and utility of such a formulation. Existence of a stable formulation may obviate the need for preparing emulsions on a daily or frequent basis. Additional mechanistic investigations, such as those evaluating sites (brain *vs.* spinal cord) of anesthetic action,[24,25] organ protection and modulation of ischemia-reperfusion injury, and neuraxial or regional anesthesia, may be facilitated.

Like many articles, the one by Jee *et al.* prompts several obvious and nonobvious questions, and points the way to future investigations by which to seek the answers. For example, what are the fate, effect, and safety of the excipients and coformulation agents in the sevoflurane emulsion? How will the pharmacokinetics and pharmacodynamics of the new IV sevoflurane compare with that of inhaled sevoflurane or other volatile anesthetics? Although emulsions can obviously change the route of volatile anesthetic administration, will they influence the route and kinetics of elimination: pulmonary clearance and exhalation? Can the new sevoflurane emulsion be used for maintenance of anesthesia? How will exhaled IV volatile anesthetics be scavenged? If an anesthetic circuit is needed for scavenging, does this obviate one potential advantage of emulsions of not needing an anesthesia machine? Or can available nonanesthesia machine-based scavenging masks, which can also provide oxygen, be used? What are the relative advantages and disadvantages of IV emulsion *versus* inhalation-based administration of volatile anesthetics? Might IV anesthetic emulsions lead to new clinical indications in addition to that for which volatile anesthetics were originally approved? We can hopefully look forward to future investigations addressing these and other questions.

In addition to the specific implications for anesthesiology research and possibly practice, the manuscript by Jee *et al.* also serves to remind us of issues relevant to innovation. Thus this editorial could have easily been titled "Sevoflurane emulsions: Informing nanoscale science and macroscale science policy." Innovation in pharmaceutical development can be considered radical or incremental, where the former involves development of new molecular entities while the latter includes supplemental indications and new formulations.[26] Another interesting aspect of the pharmaceutical innovation published by Jee *et al.* is that it comes from an academic laboratory.

Should academic anesthesia be engaged in pharmaceutical development? Should academia in general? Indeed, the role of academia in innovation, entrepreneurship, and commercialization is currently controversial. Is this like getting oil and water to mix? "Purists" may argue that academia is the domain of basic, rather than applied, research. Nevertheless, logic and evidence contravene such contentions. Whereas early constructs considered basic and applied research either exclusive and in conflict, or arrayed on either ends of a linear one-dimensional continuum, more informed paradigms consider them dynamic and intertwined.[27] University innovation and technologies result in the introduction of hundreds of new products to the marketplace and billions of dollars of benefit to the U.S. economy annually, and the creation of more than one new startup company per day.[28] Indeed, approximately one-third of the scientifically innovative drugs approved by the U.S. Food and Drug Administration from 1998 to 2007 were initially discovered in universities.[29] Moreover, applied and commercialization research does not detract from traditional academic missions. Research shows that intellectual property creation and commercialization does not make faculty less likely to publish (on the contrary, they are more prolific), shift effort away from fundamental research toward more applied research, significantly delay publication, or replace scholarly output and quality as principal criteria for academic employment and advancement.[28] The research and the report by Jee *et al.*, together with the publication record of these investigators, confirm these contentions. Other academic anesthesia laboratories have likewise contributed to radical or incremental pharmaceutical innovation with commercialization potential,[30–32] and such endeavors are to be encouraged.

In summary, the report by Jee *et al.* describes a new, enabling technology for the formulation of sevoflurane, and perhaps other, volatile anesthetic emulsions, which are stable when stored for up to a year. Such emulsions can be administered intravenously to rapidly achieve general anesthesia. Other potential applications may also be discovered. We look forward to additional investigations of volatile anesthetic emulsions.

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