2007 in Review: A Dozen Steps Forward in Anesthesiology

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SIMPLE, practical methods to improve postoperative pain control. Shifting our focus about where and when women die in childbirth from anesthesia. Blood tests to predict morbidity and mortality in our patients. Where and how anesthetics work. What method to choose in performing a regional anesthetic block. Whether to continue using nitrous oxide. These issues should be of interest to all medical practitioners in our specialty. Our goal in this short review was to highlight these and a few other articles that reflect the best articles published in ANESTHESIOLOGY in 2007.

How to choose the best? We used a simple approach, employing our mission statement. Journals, like all organizations, have a mission. The mission of ANESTHESIOLOGY, as defined in lengthy discussions of the Editorial Board of the Journal in 2007, is “to advance the science and practice of perioperative, critical care, and pain medicine through the promotion of seminal discovery.”

We advance science and practice by encouraging and publishing important and novel findings, and we promote them through reviews such as this as well as other communications in print, on the Internet, and to the press. The following dozen articles were thought by the Editors, Associate Editors, and Editor-in-Chief to most effectively meet the mission of the Journal. Not surprisingly, the diversity of articles selected reflects the general mix that undergoes rigorous peer review and is published in ANESTHESIOLOGY. In this year are four laboratory and eight clinical investigations submitted from eight countries on three continents. Their subject matter spans the gamut of investigation in our specialty, and such, the only clear theme in this review is that of excellence in meeting our mission.


Considerable effort is being made to reduce or eliminate pain in postoperative patients. Despite this effort, the search for such drugs or drug combinations has not been highly successful. Many trials use non-opioid analgesics in an attempt to improve pain control, as measured by a reduction in postoperative pain scores, and to reduce opioid-induced side effects by reducing opioid doses. Lavand’homme and colleagues administered a continuous infusion of diclofenac, a nonsteroidal antiinflammatory drug, for 48 h through a catheter implanted under the fascia in the wound of women after cesarean section. Not only was pain reduced, but morphine consumption was also decreased by 50% (fig. 1). Parenteral administration of the same dose of diclofenac was not as effective. This study suggests that doses of nonsteroidal antiinflammatory drugs administered locally are associated with greater analgesic efficacy compared with parenteral administration and emphasizes local mechanisms for acute pain control at its source. Treatments for postoperative pain that are directed locally may have not only greater efficacy but also reduced systemic side effects.

Fig. 1. Greater reduction in postoperative morphine use via patient-controlled analgesia (PCA) by wound infusion of diclofenac versus ropivacaine. * P < 0.05 compared with saline. Modified with permission from Lavand’homme et al, ANESTHESIOLOGY 2007; 106:1220–5.
Lim TKY, MacLeod BA, Ries CR, Schwarz SKW: The quaternary lidocaine derivative, QX-314, produces long-lasting local anesthesia in animal models in vivo. Anesthesiology 2007; 107:305–11

Blocking pain in the periphery, either at nerve endings with local or topical treatment or around axons with peripheral nerve injection, avoids many of the side effects of centrally acting agents. We rely almost exclusively on traditional local anesthetics to do this, yet these can enter the central nervous system, resulting in seizures or, at high circulating concentrations, producing cardiotoxicity. QX-314, a quaternary lidocaine derivative with a permanent charge, failed to produce blockade of electrical activity of neuronal preparations in vitro, leading to the conclusion that local anesthetics must traverse the cell membrane to block sodium channels and act as anesthetics. Lim and colleagues revisited this compound and observed in three in vivo animal models with local or peripheral nerve injection that QX-413 does indeed produce local anesthesia, and it does so with a remarkably long duration (fig. 2). We chose this article because it rigorously challenged dogma, based on in vitro evidence, that such molecules could not produce local anesthesia. This publication in Anesthesiology preceded by 3 months a publication in Nature that also demonstrated that, under certain conditions, QX-413 could indeed act as a local anesthetic in vivo. There are clear discrepancies between these two reports that require further research. Nonetheless, these studies shift our thinking regarding local anesthetics and could lead to development of a different class of local anesthetics that fail to penetrate the central nervous system or to produce cardiotoxicity.

The popularity and application of regional anesthesia has exploded in the last 2 decades. This paralleled and likely reflected the introduction of nerve stimulation and later, ultrasonography, to more easily and quickly guide its successful performance. As a result of this evolution, many teaching programs worldwide have greatly expanded the exposure anesthesia residents receive to regional anesthesia. Faculty of teaching programs include advocates of peripheral nerve stimulation and ultrasonography, and there has been a recent and vigorous debate regarding which of these methods is preferred for teaching and for clinical application of regional anesthesia. Many individuals have argued that ultrasonography will selectively enhance success rates and reduce the incidence of complications because of its superior and direct ability to guide the performance of peripheral blocks. This question was challenged by Casati and colleagues, who compared neurostimulation and ultrasonography after multiple injection axillary brachial plexus block. The authors clearly demonstrated that, in experienced hands, the major outcomes for performing a single-shot nerve block are similar between the two techniques. Thus, although this study does not address the relative benefits of these techniques in other situations, including teaching beginning residents or the insertion of perineural catheters, it concludes that for individuals with experience with the two techniques, there is no difference in outcome with a single injection block.


Evaluating postoperative cardiac patients for infections can be difficult because cardiopulmonary bypass itself induces a nonspecific inflammatory response. Therefore, having a biomarker that is specific for infection would be particularly useful in this patient population. Jebali and colleagues performed a single-center prospective study of 100 patients scheduled for elective cardiac surgery. Patients were excluded if they had a preoperative infection or if they were receiving corticosteroids. All patients received the same anesthetic and the same antibiotic prophylaxis for 24 h. Baseline blood samples were obtained after induction of anesthesia and after cardiopulmonary bypass. Daily postoperative tests for the first week were done for procalcitonin, C-reactive protein, neutrophil counts, and IL-6 and IL-8. Procalcitonin was significantly increased in patients with infections and was considerably more accurate than any other test evaluated (fig. 3). However, procalcitonin and all the other biomarkers were elevated for the first 2 days and therefore were not useful for diagnosing infections during this period. After the second postoperative day, a value of procalcitonin >1.5 ng/ml was strongly predic-
tive of an infectious complication. Confirmation of these seminal findings in a larger group of patients and institutions could lead to widespread use of this biomarker to aid in the important clinical diagnosis of infection in these patients.


Another study in the Journal provided clear evidence for a different biomarker for outcome in the critically ill. Protein C is part of the natural anticoagulant system that is activated as part of the host response to infection. Brunkhorst and colleagues demonstrated that protein C concentrations were below the lower limit of normal in approximately 50% of 312 consecutive surgical patients admitted to the intensive care unit and that these continued to decrease in many individuals in the subsequent days after surgery. Low protein C concentrations were correlated with increased risk of developing organ failure, sepsis, and mortality (fig. 4) and were as predictive for death as commonly used scoring systems such as Acute Physiology and Chronic Health Examination II and Simplified Acute Physiology Score. Based on these findings, protein C concentrations hold promise as a new indicator of the severity of illness and risk of intensive care unit mortality in critically ill patients. The authors suggest that protein C may also be a new target for therapy of patients with noninfection-induced organ dysfunction/failure. This work is particularly important because previous studies did not focus on surgical patients in whom critical illness and/or sepsis had not yet developed. The findings of Brunkhorst and colleagues may have considerable impact on our understanding of the development of critical illness and its relation to protein C. These findings may help to identify patients who are at risk of developing severe illness and organ failure at an early stage.


Congestive heart failure results initially in an increase in pulmonary venous pressure, which can lead to a series of vascular responses that culminate in pulmonary arterial hypertension, right ventricular failure, and death. Clinical trials of orally administered vasodilators failed to reduce mortality in these patients, and there was some evidence that these agents increased mortality. Very preliminary clinical observations suggest that inhaled vasodilator therapy may be beneficial in this setting, but its role has not been adequately investigated at either the laboratory or clinical level. Hentschel and colleagues used a rat model of congestive heart failure to demonstrate that inhaled milrinone, a phosphodiesterase-3 inhibitor vasodilator, reduces pulmonary hypertension and, therefore, right ventricular afterload (fig. 5). They further demonstrated a sustained reduction of pulmonary arterial pressure and edema formation by repetitive milrinone inhalations with no detection of left ventricular volume overload. In contrast to the predominant action of inhaled milrinone on the pulmonary vascula-
ture, intravenous infusion of milrinone resulted in systemic vasodilatation. Clearly, patients with congestive heart failure may benefit from vasodilatory therapeutic approaches to reduce pulmonary vascular resistance. Based on this study, inhaled milrinone may present an effective new treatment strategy in pulmonary venous hypertension to unload the right ventricle and reduce edema formation. Hentschel and colleagues have provided anesthesia, critical care, and medicine clinicians with a clear rationale for further trials that would test the impact of inhaled milrinone in patients with pulmonary venous hypertension resulting from congestive heart failure.


The ability of volatile anesthetic agents to precondition the heart against myocardial ischemia and reperfusion injury was demonstrated in animal models more than a decade ago. Numerous randomized clinical trials subsequently established the beneficial effects of volatile anesthetics to improve left ventricular function and decrease troponin release in patients undergoing on- and off-pump coronary artery surgery. Lucchinetti and colleagues applied state-of-the-art gene expression profiling techniques to identify regulatory mechanisms that mediate volatile anesthetic cardioprotection in patients during cardiac surgery. These investigators demonstrated that short-term administration of anesthetics differentially activated the transcriptional response to cardiac surgery and that volatile anesthetics modulated myocardial energy metabolism pathways. As such, sevoflurane, compared with propofol, reduced transcriptional activity in the fatty acid oxidation pathway and in the DNA damage signaling pathway and increased transcriptional activity in the granulocyte colony-stimulating factor survival pathway (fig. 6). These differences in transcriptional activation between sevoflurane and propofol predicted clinical differences between these treatments in N-terminal pro-brain natriuretic peptide release, cardiac index, and diastolic heart function. These findings support recent experimental evidence indicating that mitochondria are critical subcellular targets of volatile anesthetic protection. The work of Lucchinetti et al provides an important step in bench to bedside, and back again, translation of laboratory findings to the operating room and thus advances the science of anesthesiology.


Nitrous oxide continues to enjoy widespread use and is considered to be safe and effective, yet there have been few large controlled trials examining its contributions to anesthetic morbidity. In a multi-center study, Myles and colleagues recruited more than 2,000 subjects undergoing surgery with an anticipated duration longer than 2 h and randomized them to receive either a nitrous oxide-based anesthetic (70% nitrous oxide, 30% oxygen) or a nitrous oxide-free anesthetic (20% nitrogen, 80% oxygen). Their primary endpoint, duration of hospital stay, did not differ between groups. This provides strong support for those who argue that nitrous oxide holds a...
valuable and routine place in anesthesia. Of their secondary endpoints, however, those who received nitrous oxide were more likely than those who did not receive it to experience severe nausea and vomiting and to have fever, wound infection, pneumonia, and atelectasis. Other studies have suggested that supplemental oxygen reduces some of these complications, and it is conceivable that the higher oxygen concentration provided to those who did not receive nitrous oxide in this trial participated in this difference. This study was accompanied by an editorial, and both were addressed by considerable correspondence. This research does not end the debate over the routine use of nitrous oxide for anesthesia. It does provide a new observation by applying appropriately controlled and designed trial design to a key endpoint, duration of hospital stay, and provides essential data for the design of future trials.


Understanding the sites of anesthetic actions has both practical as well as scientific benefits. In this study Velly and colleagues took advantage of the ability to record electrical activity in deep brain structures in patients with Parkinson disease who had deep brain electrodes in place and who were coming to surgery for other reasons. By recording from these electrodes as well as the surface electroencephalogram, they were able to quantify the relationship between surface and deep electrical activity during anesthesia induction as it relates to loss of consciousness and lack of movement to a noxious stimulus. They observed that change in surface electroencephalographic activity, but not deep brain electrical activity, correlated with loss of consciousness during anesthetic induction (fig. 7A). These data support the concept that monitoring brain surface electrical activity may be useful to gauge conscious state, and all marketed products that attempt to provide this rely on measuring precisely this activity. Of course, this study does not address the question of whether such devices or measuring brain surface electrical activity would prevent awareness. In contrast to the correlation with consciousness, prevention of movement correlated with drug effects on the electrical activity of deep, but not superficial, areas of the brain (fig. 7B). Other publications in Anesthesiology in 2007 and before have also highlighted the importance of the thalamus and the spinal cord in this primary effect of anesthesia.


Several lines of evidence suggest that a primary site of action of anesthetics is at γ-aminobutyric acid type A (GABA_A) receptors. Curiously, closely related anesthetics may differ in the specifics of this interaction. In this study, Sonner and colleagues utilized genetically altered mice that carried mutations of the GABA_A receptor,
known to alter their sensitivity to some anesthetics. They examined the effects of volatile anesthetics on in vitro and in vivo responses. These mice carried mutations specifically in a commonly expressed subunit of the GABA<sub>A</sub> receptor, the α1 subunit. Interestingly, they showed that mice with the altered α1 subunit exhibited an amnestic response to isoflurane similar to wild type mice in a memory task in vivo, yet the mutated mice showed a reduced action of isoflurane in hippocampal neurons in vitro. This fascinating result suggests that direct effects of isoflurane in the hippocampus on this subunit of GABA<sub>A</sub> receptors are not important to amnesia from this agent, as they certainly are for benzodiazepines, and that other sites, such as the amygdala, should be examined regarding amnesia from this agent. MAC from several volatile anesthetics, including isoflurane, was unaffected by this mutation of the α1 subunit of GABA<sub>A</sub> receptors, consistent with observations by others that this aspect of anesthesia likely reflects a primary action in the spinal cord, where GABA<sub>A</sub> receptors are not abundant. Finally, the loss of righting reflex, a measure of hypnosis, was affected differentially by this mutation of the α1 subunit of GABA<sub>A</sub> receptors, with a reduction in the potency of isoflurane and enflurane, but not halothane, in mutated mice. Taken together, these data significantly further focus our attention on the remarkable variability in the action of clinically similar anesthetics on GABA<sub>A</sub> receptors.


Chronic pain is often associated with a sensitization to both innocuous and noxious peripheral stimuli, and much of this sensitization is thought to occur at the spinal cord level. When a peripheral nerve is intensely stimulated, such as may occur during surgery, or is injured, such as from trauma, diabetes, chemotherapy, or cancer, it releases several substances in the spinal cord, which can lead to sensitization. One of these is calcitonin gene-related peptide (CGRP), and this was the target of this study by Tzabazis and colleagues. They took advantage of the affinity of the herpes virus for peripheral nervous tissue to alter the ability of nerves to release CGRP. In their study, Tzabazis et al applied a recombinant herpes vector that encoded an antisense sequence to the CGRP gene onto the skin of the rat paw. They demonstrated that this was taken up by the nerves innervating the paw and that it resulted in reduced expression of CGRP by these sensory afferents. Not only did this reduction in the ability of sensory afferents to synthesize and release CGRP produce analgesia to an acute noxious stimulus (heat), but it also significantly reduced generation of sensitization from intense noxious stimulation via application of capsaicin to the paw.

Although this same effect could be briefly produced by spinal injection of a CGRP receptor antagonist, their most remarkable observation was that this protection against sensitization lasted for many weeks after a single topical administration of the herpes vector (fig. 8). This clever variant of gene therapy not only provides additional information regarding the central role of CGRP in sensitized states, but also provides strong rationale for further examination of this approach in humans with chronic pain.


Maternal death from anesthesia is now rare, thanks in part to large population studies examining the causes of maternal death. This article examines anesthesia-related maternal mortality from only one state in only one country, but it provides a unique opportunity in that original records could be obtained in all cases. In this milestone study, Mhyre and colleagues demonstrate that no maternal deaths occurred during induction of anesthesia and loss of the airway in Michigan in this 18-yr period. This is important because previous maternal mortality studies had identified general anesthesia and failure to secure the airway as important problems, and the period of anesthetic induction has been the focus of considerable education within the subspecialty of obstetric anesthesia. Rather than at induction of anesthesia, women in the Michigan study died as a result of hypoventilation or airway obstruction during emergence, extubation, or recovery, as well as during the postoperative period. This work confirms the importance of vigilance throughout the perioperative period, including the time during which postoperative analgesics are administered, and
will likely lead to new efforts to further reduce mortality
during childbirth.

Summary

These 12 articles represent an inspiring collection of
advances in our specialty. Yet another dozen could easily
have been chosen, including:

- Long-term neuroprotection from isoflurane: Sakai et al.
  Anesthesiology 2007; 106:92–9
- The first human application of a novel local anesthetic:
  Rodríguez-Navarro et al. Anesthesiology 2007; 106:
  339–45
- Application of monitoring to measure in real time end-
tidal concentrations of systemically administered
  drugs: Takita et al. Anesthesiology 2007; 106:659–64
  and Hornuss et al. Anesthesiology 2007; 106:665–4
- ASA practice guidelines for obstetric anesthesia: Con-
nis et al. Anesthesiology 2007; 106:843–63
- The safety of low dose droperidol in the peri-operative
- Moving neuromuscular monitoring electrodes 2 cm
  medially reduces the incidence of postoperative nau-
  sea and vomiting as much as pharmacologic therapy:
- Laboratory studies suggesting a drug used orally to
  treat Alzheimer’s disease might also be used to treat
  chronic pain: Clayton et al. Anesthesiology 2007; 106:
  1019–25
- Novel description of an anesthetic site of action on
  presynaptic targets: Metz et al. Anesthesiology 2007;
  107:971–82

Just as movie trailers are intended to whet your appe-
tite to see a film, so do we hope this brief review
highlighting practical and theoretical advances in the
practice of medicine in our specialty will whet your
appetite to reread these articles. Stay tuned for 2008!

Reference

1. Binshtok AM, Bean BP, Woolf CJ: Inhibition of nociceptors by TRPV1-
mediated entry of impermeant sodium channel blockers. Nature 2007; 449:
607–10.