



ON THE COVER:

The best proven approach to predicting response to surgical stimulation under general anesthesia is use of pharmacokinetic–pharmacodynamic (PK/PD) models for opioids and hypnotics. An alternative approach is based on the individual assessment of a physiologic reflex evoked by a standardized noxious test. In this issue of *ANESTHESIOLOGY*, Guglielminotti *et al.* demonstrate that the pupillary dilatation reflex amplitude is as accurate as use of PK/PD models for predicting movement in response to surgical stimulation. In an accompanying Editorial View, Larson and Gupta tell us how pupillometry may bring us a step closer to tailoring anesthesia in real-time to meet the needs of each individual patient.

- Guglielminotti *et al.*: Prediction of Movement to Surgical Stimulation by the Pupillary Dilatation Reflex Amplitude Evoked by a Standardized Noxious Test, p. 985
- Larson and Gupta: Pupillary Reflex Dilation to Predict Movement: A Step Forward Toward Real-time Individualized Intravenous Anesthetics, p. 961

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SPECIAL ARTICLES

- ◆◆ **Safeguards to Prevent Neurologic Complications after Epidural Steroid Injections: Consensus Opinions from a Multidisciplinary Working Group and National Organizations** 974
J. P. Rathmell, H. T. Benzon, P. Dreyfuss, M. Huntoon, M. Wallace, R. Baker, K. Daniel Riew, R. W. Rosenquist, C. Aprill, N. S. Rost, A. Buvanendran, D. Scott Kreiner, N. Bogduk, D. R. Fournay, E. Fraifeld, S. Horn, J. Stone, K. Vorenkamp, G. Lawler, J. Summers, D. Kloth, D. O'Brien, Jr., and S. Tutton

Epidural corticosteroid injections can lead to rare, catastrophic neurologic injuries. Seventeen clinical considerations aimed at improving safety were produced by stakeholder societies. Adherence to specific recommended practices should lead to a reduction in the incidence of neurologic injuries.

PERIOPERATIVE MEDICINE

CLINICAL SCIENCE

- ◆◆ **Prediction of Movement to Surgical Stimulation by the Pupillary Dilatation Reflex Amplitude Evoked by a Standardized Noxious Test** 985
J. Guglielminotti, N. Grillot, M. Paule, F. Mentré, F. Servin, P. Montravers, and D. Longrois

Seventy-six women scheduled for an operative procedure requiring cervical dilation were anesthetized with a target propofol effect-site concentration of 4 µg/ml with a randomly assigned remifentanyl effect-site concentration of 0, 1, 3, or 5 ng/ml. Pupillary dilatation reflex amplitude in response to a standardized noxious test predicted movement response on cervical dilation as accurately as the estimated remifentanyl effect-site concentration.

- ◆🌐 **Corneal Abrasion in Hysterectomy and Prostatectomy: Role of Laparoscopic and Robotic Assistance** 994
A. Sampat, I. Parakati, R. Kunnavakkam, D. B. Glick, N. K. Lee, M. Tenney, S. Eggener, and S. Roth

In a review of nearly 1 million prostatectomy and hysterectomy cases from the National Inpatient Sample, corneal abrasion was not increased with robotic-assisted prostatectomy. Compared with open hysterectomy, risk of corneal abrasion was increased nearly fourfold with the laparoscopic technique and nearly 6.5-fold with the robotic technique. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

- Pharmacokinetics of ε-Aminocaproic Acid in Neonates Undergoing Cardiac Surgery with Cardiopulmonary Bypass** 1002
M. P. Eaton, G. M. Alfieris, D. M. Sweeney, R. E. Angona, J. M. Cholette, C. Venuto, and B. Anderson

ε-Aminocaproic acid clearance, expressed using allometry, is reduced in neonates undergoing elective cardiac surgery compared with older children and adults. Loading dose and infusion dose are approximately half those required in children and adults.

- Modeling the Anesthetic Effect of Ropivacaine after a Femoral Nerve Block in Orthopedic Patients: A Population Pharmacokinetic–Pharmacodynamic Analysis** 1010
F. Gaudreault, P. Drolet, M. Fallaha, and F. Varin

A population pharmacokinetic–pharmacodynamic model was developed that describes the relationship between sensory response and the amount of ropivacaine remaining at the site of injection after single-dose injection for femoral nerve block. Simulation using the model suggests that following a bolus dose of 100 mg, 0.2% ropivacaine hydrochloride should be infused at least at 3 ml/h to maintain a complete sensory block for 48 h.

- 🌐 **H Predictors of Clinically Significant Postoperative Events after Open Craniosynostosis Surgery** 1021
S. M. Goobie, D. Zurakowski, M. R. Proctor, J. G. Meara, P. M. Meier, V. J. Young, and G. F. Rogers

Children undergoing craniosynostosis surgery are at increased risk for clinically significant postoperative events requiring intensive care unit admission if they are less than 10 kg body weight, American Society of Anesthesiologists physical status 3 or 4, require intraoperative transfusion of greater than 60 ml/kg of packed erythrocytes, receive hemostatic blood products, or if they develop a significant intraoperative complication. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

Next-generation Sequencing of *RYR1* and *CACNA1S* in Malignant Hyperthermia and Exertional Heat Illness

1033

D. Fiszer, M.-A. Shaw, N. A. Fisher, I. M. Carr, P. K. Gupta, E. J. Watkins, D. Roiz de Sa, J. H. Kim, and P. M. Hopkins

Variants in the ryanodine receptor gene were identified in 13 of 29 malignant hyperthermia patients, with one variant in Cav1.1. Targeted DNA sequencing is a potentially useful diagnostic approach to identifying genetic variants associated with malignant hyperthermia and exertional heat illness.

BASIC SCIENCE

◆ Impact of Hyperpolarization-activated, Cyclic Nucleotide-gated Cation Channel Type 2 for the Xenon-mediated Anesthetic Effect: Evidence from *In Vitro* and *In Vivo* Experiments

1047

C. Mattusch, S. Kratzer, M. Buerge, M. Kreuzer, T. Engel, C. Kopp, M. Biel, V. Hammelmann, S.-W. Ying, P. A. Goldstein, E. Kochs, R. Haseneder, and G. Rammes

In thalamocortical slices, xenon evoked hyperpolarization-activated, cyclic nucleotide-gated cation (HCN) channel-dependent impairment of neuronal excitability and reduced thalamocortical signal propagation. In HCN2 knockout mice, the sedative effect of xenon was not observed. The data suggest that depression of thalamocortical signal propagation that is in part mediated by HCN2 channels might contribute to the anesthetic action of xenon.

🌐 Syntrophin-mediated Resistance and Hypersensitivity to Isoflurane in *Drosophila melanogaster*

1060

O. H. Zalucki, H. Menon, B. Kottler, R. Faville, R. Day, A. T. Bademosi, N. Lavidis, S. Karunanithi, and B. van Swinderen

Isoflurane targets synaptic release mechanisms in addition to sleep pathways in flies. Different mutations in syntrophin confer resistance and hypersensitivity across multiple behavioral and electrophysiological endpoints in flies. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

■ CRITICAL CARE MEDICINE

BASIC SCIENCE

📖 Anesthesia with Disuse Leads to Autophagy Up-regulation in the Skeletal Muscle

1075

A. Kashiwagi, S. Hosokawa, Y. Maeyama, R. Ueki, M. Kaneki, J. A. J. Martyn, and S. Yasuhara

Using Western blotting and histology in mice, it was found that short-term disuse without anesthesia did not lead to autophagy, but anesthesia with disuse leads to marked up-regulation of autophagy.

🌐 Synergistic Inhibition of β_2 -adrenergic Receptor-mediated Alveolar Epithelial Fluid Transport by Interleukin-8 and Transforming Growth Factor- β

1084

B. M. Wagener, J. Roux, M. Carles, and J.-F. Pittet

In human and rat alveolar epithelial cells, combined exposure to interleukin-8 and transforming growth factor- β 1 synergistically inhibited β_2 -adrenergic agonist-mediated Cl^- transport, important to fluid removal. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

Norepinephrine Decreases Fluid Requirements and Blood Loss While Preserving Intestinal Villi Microcirculation during Fluid Resuscitation of Uncontrolled Hemorrhagic Shock in Mice

1093

A. Harrois, N. Baudry, O. Huet, H. Kato, L. Dupic, M. Lohez, M. Zioli, E. Vicaut, and J. Duranteau

The administration of both norepinephrine with crystalloid (normal saline [NS]) led to less fluid requirements than when animals only received NS to reach a target blood pressure. There was also no significant difference in the intestinal villi microcirculatory perfusion in the animals resuscitated with NS alone compared to animals given NS and norepinephrine.

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CLINICAL SCIENCE

- ◆◆ **Fibromyalgia Survey Criteria Are Associated with Increased Postoperative Opioid Consumption in Women Undergoing Hysterectomy** 1103

A. M. Janda, S. As-Sanie, B. Rajala, A. Tsodikov, S. E. Moser, D. J. Clauw, and C. M. Brummett

In 208 women undergoing hysterectomy, higher scores on a fibromyalgia survey were independently associated with increased opioid consumption after accounting for known risk factors. This fibromyalgia survey may be useful in identifying individuals at high risk for increased opioid consumption after surgery.

- ◆◆ **Intraoperative Methadone for the Prevention of Postoperative Pain: A Randomized, Double-blinded Clinical Trial in Cardiac Surgical Patients** 1112

G. S. Murphy, J. W. Szokol, M. J. Avram, S. B. Greenberg, J. H. Marymont, T. Shear, K. N. Parikh, S. S. Patel, and D. K. Gupta

Intraoperative methadone administration may be superior to intraoperative fentanyl for the control of pain during the 24-h period following cardiac surgery. The superior pain control provided by methadone does not appear to involve a higher likelihood of opioid-related adverse events in this setting.

- CME ◆◆ **Genetic and Clinical Factors Associated with Chronic Postsurgical Pain after Hernia Repair, Hysterectomy, and Thoracotomy: A Two-year Multicenter Cohort Study** 1123

A. Montes, G. Roca, S. Sabate, J. I. Lao, A. Navarro, J. Cantillo, and J. Canet; for the GENDOLCAT Study Group

Persistent postoperative pain was diagnosed in 18% of a population-based sample of 2,929 patients who had hernia repairs, hysterectomies, or thoracotomies. The association of persistent pain with 90 genetic markers showed no evidence for genetic predisposition in a subset of 1,000 patients. Six clinical factors predicted 73% of the persistent pain that developed. *SUPPLEMENTAL DIGITAL CONTENT IS AVAILABLE IN THE TEXT*

BASIC SCIENCE

- Up-regulation of CX3CL1 via Nuclear Factor- κ B-dependent Histone Acetylation Is Involved in Paclitaxel-induced Peripheral Neuropathy** 1142

D. Li, Z.-Z. Huang, Y.-Z. Ling, J.-Y. Wei, Y. Cui, X.-Z. Zhang, H.-Q. Zhu, and W.-J. Xin

Using a rat model of paclitaxel-induced neuropathy, both pharmacological and small interfering RNA-based techniques showed that CX3CL1 supports allodynia in this model. Chromatin immunoprecipitation experiments demonstrated that an epigenetic mechanism controls CX3CL1 expression in the spinal neurons of neuropathic rats.

■ EDUCATION

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S. C. Youngblood and H. R. Baig

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A. Nader and M. C. Kendall

ORIGINAL INVESTIGATIONS IN EDUCATION

- ◆ **Practice Improvements Based on Participation in Simulation for the Maintenance of Certification in Anesthesiology Program** 1154

R. H. Steadman, A. R. Burden, Y. Ming Huang, D. M. Gaba, and J. B. Cooper

In a review of 634 Maintenance of Certification in Anesthesiology Program simulation course participants, 94% successfully implemented some or all of their planned practice improvements, which focused mostly around environment or systems changes, teamwork skills, and personal knowledge.

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J. Brainard, M. Gobel, B. Scott, M. Koeppen, and T. Eckle

This paper reviews the molecular basis of circadian rhythms and the pathophysiologic consequences of alterations in these rhythms, and explores the concept of daylight as therapy to restore disrupted circadian rhythms and improve clinical outcomes.

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