Effects of Sevoflurane and Halothane on Children’s Postoperative Behavior and Sleep Patterns. Kain et al. (page 720)

Is sevoflurane anesthesia, used widely in pediatric surgical anesthesia, more likely to cause emergence delirium and postoperative maladaptive behavioral changes? To explore this issue, Kain et al. recruited children aged 3–10 yr and their parents to participate in a double-blind, randomized, controlled trial. During preoperative orientation sessions, parents received an informational study packet containing an actigraph (a wrist device that digitally records sleep and wakefulness), baseline questionnaires, and a sleep diary with which to record the child’s sleep and wake times. Children wore the actigraphs at night for five nights before their surgeries. On the day of surgery, parents completed the State Trait Anxiety Inventory, and the children were also assessed for their levels of preoperative anxiety. Fifty children were assigned to receive halothane anesthesia, and 52 to receive sevoflurane. All parents, children, and research assistants who gathered outcomes data were blinded to group assignment.

After their surgical procedures, children were monitored and assessed for incidence of emergence delirium and their levels of pain. Before discharge from the hospital, parents were instructed to follow postoperative medication instructions (which included administration of acetaminophen alone or with codeine), to keep daily sleep logs, and to attach the actigraph to their child’s wrist 1 h before bedtime each night. Families were contacted by phone on each of the five nights after surgery.

Results showed no differences in preoperative state anxiety, postoperative analgesic requirements, postoperative pain, or incidence of emergence delirium between the two groups. Analyzing results of the Post Hospitalization Behavioral Questionnaire, the researchers found no group differences in results from subscales of the questionnaire which assess general anxiety, eating patterns, apathy and withdrawal, sleep, social anxiety, and aggression against authority. The use of sevoflurane was not associated with higher incidence of emergence delirium, new-onset maladaptive postoperative behavioral changes, or sleeping problems.

Mechanisms of Benzodiazepine Action Explored. Rüsch and Forman (page 783)

Rüsch and Forman designed a series of electrophysiological experiments to investigate the mechanisms by which benzodiazepines modulate the activity of γ-aminobutyric acid (GABA) receptors. To shed light on conflicting data regarding benzodiazepines’ binding and GABA receptor activity, the team used γ-aminobutyric acid type A (GABA_A) receptors recombiantly expressed in Xenopus oocytes. To test gating effects in the absence of an orthosteric agonist, the team used spontaneously active GABA_A receptors containing a leucine-to-threonine mutation at residue 264 on the α_1 subunit. To test effects of gating when orthosteric sites were fully occupied, the team activated normal, wild-type receptors with high concentrations of a partial agonist, piperidine-4-sulfonic acid. The team found that midazolam increases the maximal efficacy of piperidine-4-sulfonic acid in normal receptors. The channel opening of the spontaneously active mutant receptors, in the absence of orthosteric agonists, was increased by diazepam and midazolam; and the mutant channel activity was reduced by the inverse benzodiazepine agonist FG7142.

Midazolam modulation of the wild-type GABA_A receptors was assessed by measuring leftward shifts in GABA concentration-responses. In the presence of 10 nm midazolam, a consistent and significant leftward shift of the GABA response curve was observed. The leftward shifts caused by the same concentration of midazolam were similar in both wild-type and mutant GABA_A receptors. Benzodiazepines, the authors suggest, act as coagonists on the gating of GABA receptors. The effect of benzodiazepines on GABA binding may not be as important. The gating model can be used to explain the difference in efficacy between benzodiazepines and anesthetics like etomidate.

Neuroprotective Gene Expression Studied in Rat Model of Traumatic Brain Injury. Hellmich et al. (page 806)

In their study of gene expression after neuronal injury in rats, Hellmich et al. randomly assigned rats to a normotensive or hemorrhagic hypotensive group after each had undergone traumatic brain injury induced via moderate parasagittal fluid percussion. Hypotension was induced by withdrawing sufficient blood to reduce mean arterial blood pressure to 40 mmHg for 45 min. Twenty-four hours after traumatic brain injury, the rats were euthanized and their brains removed for sectioning and staining with 1% cresyl violet and 0.001% Fluoro-Jade. Using laser capture microdissection, the team obtained
RNA from 10 Fluoro-Jade-positive neurons and 10 Fluoro-Jade-negative neurons from each rat’s CA1, CA3, and dentate gyrus hippocampal subregions.

The team then used ribonuclease protection assay analysis to quantitatively compare mRNA expression for nine neuroprotective and apoptosis-related genes in injured versus noninjured neurons. In injured CA3 neurons, they found expression of the neuroprotective genes glutathione peroxidase 1, heme oxygenase 1, and brain-derived neurotrophic factor was significantly decreased. Hemorrhagic hypotension was associated with down-regulation of neuroprotective genes in both injured and noninjured neurons of all the hippocampal subregions. The expression of apoptosis-related genes did not vary between injured and noninjured neurons, whether or not the rats had undergone hemorrhagic hypotension. Further studies of injury-induced neuronal gene expression will help elucidate the molecular determinants of neuronal survival after traumatic brain injury.

- Efficacy and Safety of Acetaminophen Injections after Orthopedic Surgery Evaluated. Sinatra et al. (page 822)

Sinatra et al. designed a repeated-dose, double-blind, placebo-controlled study to compare intravenous acetaminophen and propacetamol, a water soluble prodrug of acetaminophen widely used in Europe, as analgesia for postoperative pain. The study was conducted in seven U.S. centers and a total of 156 patients were enrolled from September 1999 to June 2000. The patients were scheduled to undergo either total hip or knee replacement procedures and received general, spinal, or epidural anesthesia. Most patients who received general anesthesia also received premedication with midazolam, and isoflurane/desflurane, fentanyl, and morphine for maintenance. Because major orthopedic surgery is extremely painful, and monotherapy with acetaminophen would not likely provide complete pain relief on the day of surgery, the study protocol was initiated the day after surgery.

Patients who reported moderate to severe pain received 1 g intravenous acetaminophen, 2 g propacetamol, or placebo at 6-h intervals over a 24-h period 1 day postsurgery. Rescue analgesia was available with patient-controlled analgesia morphine. Blinded observers monitored patients’ pain intensity, pain relief, and morphine use at specified intervals. A total of 151 patients were available for final evaluation, 49 of whom received the acetaminophen, 50 who received propacetamol, and 52 who received placebo. Those who received intravenous acetaminophen and propacetamol used significantly less morphine over the 24-h study period. These patients also demonstrated longer time to use of the first rescue medication (3 h for the acetaminophen group, 2.6 h for the propacetamol group, and 0.8 h for the placebo group). Local adverse events, including pain at the infusion site, were mostly associated with the propacetamol injections. The incidence of local adverse events with intravenous acetaminophen was similar to that shown in the placebo group. Due to the efficacy and safety shown here, the authors suggest that intravenous acetaminophen has the potential to become a useful component of multimodal postsurgical pain management.

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