◇ This Month in

ANESTHESIOLOGY

■ Safety of Low-flow Sevoflurane in Patients with Chronic Renal Insufficiency. Conzen *et al.* (page 578)

Exposure of patients to compound A, formed when sevoflurane is degraded by carbon dioxide absorbents, increases when fresh gas flow rates are reduced and compound A concentrations rise within the circuit. To address concerns about the use of low-flow sevoflurane in these patients, Conzen *et al.* enrolled 132 participants in their multicenter, multinational, open-label, randomized trial.

Patients were eligible for participation if their renal insufficiency was classified as stable, *i.e.*, serum creatinine concentration at 1.5 mg/dl or more and ASA physical status II–IV. Among other criteria, history of hemodialysis or transient renal impairment excluded patients from the study. Prior to anesthesia, patients were randomized to receive either sevoflurane or isoflurane at 1 l/min or less. Anesthesia was induced according to each site's standard procedure. End-tidal concentrations were adjusted to remain within 0.8–2.5 vol% for sevoflurane, and at 0.5–1.4 vol% for isoflurane. Use of opioids was kept to a minimum, and Baralyme® was used to increase compound A exposure. Inspiratory and expiratory compound A levels were measured at 30-min intervals during anesthesia. Blood samples were taken preoperatively, at the end of anesthesia, and at regular intervals until 72 h after anesthesia. Urine samples were also obtained at three different time points.

A total of 116 patients were able to be evaluated at the conclusion of the study. Total sevoflurane doses tended to be lower than isoflurane doses because of slightly shorter duration of surgery. The average study drug dose was 3.1 ± 2.4 MAC · h for sevoflurane and 3.8 ± 2.6 for isoflurane. Maximum inspiratory compound A with sevoflurane was 18.9 ± 7.6 ppm, resulting in an average total compound A exposure of 44.0 ± 30.6 ppm · h. There were no statistically significant changes from baseline to 24- or 72-h values for serum creatinine or blood urea nitrogen, creatinine clearance, or urine protein and glucose; nor were there significant differences between the two groups of patients. Further deterioration of renal function was seen in 12% of patients from the sevoflurane group and 14% of patients from the isoflurane group. In most of these patients, other factors were present (infusion of nephrotoxic drugs or contrast agents; major surgery) that could explain their renal function deterioration. Overall, however, there was an absence of clinically significant postoperative deterioration of preexisting renal insufficiency, and measures of renal function remained stable during the postoperative period. Low-flow sevoflurane, the authors conclude, is safe in patients with chronically impaired renal function.

■ Does Clomethiazole Provide Neuroprotection during Coronary Artery Bypass Surgery? Kong *et al.* (page 585)

Although clomethiazole—a GABA agonist, sedative and anticonvulsive—has demonstrated neuroprotective properties during forebrain ischemia in animal models, its ability to confer such protection in humans has not been investigated. Kong *et al.* recruited 245 patients scheduled for coronary artery bypass graft surgery at two centers (one in the US and another in the UK) for their prospective, double-blind, randomized trial. The investigators assessed patients' neuropsychologic performance and mood 1 day before and 4–7 weeks after surgery. They used a battery of neuropsychologic tests to assess domains of attention and concentration, visuomotor skills, visual memory, and verbal memory. The Spielberger State-Trait Anxiety Inventory and Center for Epidemiologic Studies-Depression scales were used to assess levels of anxiety and depression.

After induction of anesthesia, patients received infusions of either clomethiazole edisylate (8 mg/ml in 0.8% sodium chloride solution) or 0.9% sodium chloride solution (the placebo). The researchers chose a target plasma concentration of 50 μM based on results from animal studies and achieved this concentration by infusing a loading dose of 225 ml over 45 min, followed by a maintenance infusion of 100 ml/h until the end of surgery. Coronary artery bypass grafting was completed during moderate hypothermic conditions (28–32°C). Plasma clomethiazole concentrations were measured from blood samples drawn immediately after the start of infusion and at regular intervals thereafter. Doppler ultrasound of the middle cerebral or common carotid artery was obtained in each patient during surgery to scan for signs of emboli.

The mean plasma concentration of clomethiazole during surgery was 66.2 μM. Time to extubation was longer in the group of patients receiving the study drug, a fact probably attributable to clomethiazole's sedative effects. Postsurgical neuropsychologic assessments were completed for 219 patients, and results showed no difference in performance on these tests between those in the placebo or study drug groups. Despite evidence from animal

studies that clomethiazole confers neuroprotection during cerebral ischemia, there appear to be no parallels in humans during coronary artery bypass graft surgery.

■ Clinical Productivity Models Studied in Academia and Private Practice Anesthesiology Groups. Abouleish *et al.* (page 608)

While most comparisons of clinical productivity between academic and private practice anesthesiology groups use "per FTE" (full-time equivalent) measurements, results can be confounded by differences in staffing ratios (concurrency). Using data collected from 20 anesthesiology groups, Abouleish *et al.* applied various other measurements of productivity to determine meaningful ways to compare productivity of academic and private practice anesthesiologists.

The investigators collected clinical activity and billing data for 1 yr from 11 private practice and 9 academic anesthesiology groups. The participants supplied total ASA units (tASA), time units (TU), and number of cases billed for 1 yr, as well as the average daily number of anesthesiologists staffing the operating rooms (OR FTE) and average daily number of sites staffed (OR sites). The productivity measurements calculated from the data included staffing ratio (concurrency), tASA/OR site, billed hours per OR site per day (hr/OR/day), cases per OR site (case/OR site), average hours per case (hr/case), tASA units billed per hour of anesthesia care (tASA/hr), and base units per case. Clinical services not billed with ASA units and provision of obstetric anesthesia care were excluded from the analysis.

The researchers found that tASA/OR site measurements were similar in both types of anesthesiology practices. Academic groups, however, worked significantly longer hours per OR site than private practice groups (median hr/OR/day 7.8 *vs.* 6.0 hr) to achieve the same level of tASA/OR site. These results were influenced by duration of surgery, with private practice groups tending toward shorter surgeries than academic groups. However, academic groups, often located in teaching hospitals, often care for indigent patient groups and must allow for supervision of residents by full-time faculty. Although these external measurement comparisons may be useful for general purposes, practice groups may also choose different key indicators for their internal management purposes. In addition, a larger national survey using these measurements might provide useful benchmarking data for planning and national policy.

■ Importance of α_2-Adrenoceptor Subtypes on Clonidine Antinociception. Duflo *et al.* (page 636)

Duflo *et al.* exposed both normal rats and those with induced peripheral nerve injury to identical mechanical stimuli before and after administration of intrathecal clonidine and ST 91, a preferential $\alpha_{2\ \text{NON-A}}$ adrenoceptor agonist. The goal for the experiments was to clarify the involvement of α_2 adrenoceptor subtypes in the antinociception of clonidine.

The team isolated and ligated spinal nerves (L5 and L6) in one group of rats and allowed them to recover for 5–7 days. Intrathecal catheters were then inserted under halothane anesthesia in this group and in a group of normal rats that did not undergo spinal ligation. For a week preceding experiments, all rats were habituated to a mechanical testing device that applies force to the hind paw. Baseline withdrawal thresholds were assessed on day 1 of the experiments. (The rats with induced nerve injury had also been assessed for withdrawal thresholds to the mechanical stimulus prior to their injury.) Animals then received cumulative dosing, at 40-min intervals, of intrathecal clonidine (19, 75, 190 nmol) or, at 60-min intervals, of intrathecal ST 91 (10, 40, 100 nmol). Threshold withdrawals to mechanical stimuli were measured 40 min after administration of clonidine and 60 min after ST 91 injection.

To further examine α_2 subtypes, the animals were given doses of BRL 44408, a selective α_{2A} adrenoceptor subtype antagonist, and ARC 239, a selective $\alpha_{2\ \text{NON-A}}$ antagonist, after injections of clonidine and ST 91.

In the noninjured animals, clonidine increased withdrawal thresholds significantly 40 min after injection. Intrathecal injection of BRL 44408 or ARC 239 inhibited clonidine's antinociceptive effect in a dose-dependent manner. Injection of 40 nmol ST 91 also increased withdrawal thresholds, and ARC 239 inhibited the antinociceptive effect, while BRL 44408 did not. In rats with peripheral nerve injury, both clonidine and ST 91 also increased the withdrawal thresholds after mechanical stimulation. However, BRL 44408 failed to inhibit the effects of clonidine or ST 91, while ARC 239 inhibited the antinociceptive effects of both drugs in a dose-dependent manner. The researchers note that their data support the theory of α_{2A} adrenoceptor's importance in the antihypersensitivity effects of clonidine in normal animals. In the presence of nerve injury, this mechanism is altered, and as indicated by these results, $\alpha_{2\ \text{NON-A}}$ adrenoceptors then become more critical to the process.

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