Residual CNS Effects of Remifentanil Revealed in Healthy Volunteers. Black et al. (page 718)

As a short-acting drug, remifentanil is often a popular choice for outpatient surgery, but little is known about possible residual effects after administration is discontinued. Black et al. recruited 10 healthy volunteers (8 men and 2 women) and conducted a placebo-controlled, double-blind, crossover trial that compared psychomotor and subjective mood effects after administration of remifentanil and alfentanil.

Study participants took part in three 5-h sessions at least 1 week apart and were instructed not to ingest food or drink for 4 h before study sessions. Subjects were told that the infusion they were about to receive might or might not contain a drug. Although aware of the possible drug combinations involved, the anesthetist monitoring the infusion was blinded as to what infusion had been prepared. Participants received either saline, remifentanil, or alfentanil over a 2-h period. Target plasma concentrations for remifentanil were 0.75, 1.5, and 3.0 ng/ml and were 16, 32, and 64 ng/ml for alfentanil. These were chosen from a study that detected a 19-fold difference in potency between the two drugs.

Analgesia was assessed using a cold-pressor test administered three times during the infusion. Researchers initiated subjective testing 20 min into each infusion, and then repeated the 10-min psychomotor and subjective testing sequence at 60 and 100 min. Tests were repeated at intervals up to 180 min after discontinuation. Subjective measures included the Addiction Research Center Inventory, a locally developed visual analog scale, a locally developed adjective checklist using items from the opiate adjective checklist, and the Drug Effects/Liking Questionnaire. Various psychomotor tests, including the Maddox Wing test, the Digit-Symbol Substitution Test and the Backward Digit Span were also included.

Although they reported feeling no drug effects, volunteers who received remifentanil were still impaired on the psychomotor tests 60 min after infusion was discontinued. At the dose ranges tested, alfentanil's effects on subjective measures, psychomotor performance, and analgesia were more mild than those observed with remifentanil. The typical side effects seen with remifentanil in this study included pruritus, dry mouth, and nausea. The alfentanil produced some changes in mood, but no side effects, suggesting that the remifentanil-to-alfentanil potency ratio is larger than 20:1, and perhaps as large as 40:1.

Does Transdermal Nitroglycerin Enhance Sufentanil's Analgesic Effects? Lauretti et al. (page 734)

Fifty-six patients scheduled for knee surgery were recruited by Lauretti et al. for a controlled study to assess whether transdermal nitroglycerin enhances intrathecal opioid analgesia with sufentanil. The study was prompted by the team's previous observations that patients with angina receiving spinal block and prophylactic nitroglycerin transdermal patches required less postoperative analgesia. Participants in the study were assigned randomly to receive spinal saline and transdermal placebo; intrathecal sufentanil and transdermal placebo; spinal saline and transdermal nitroglycerin; or a combination of sufentanil and transdermal nitroglycerin. (One subject was later excluded from results analysis because of failure of the first spinal block.)

After premedication with intravenous midazolam (0.05 to 0.1 mg/kg) and 15 mg bupivacaine, patients received 2 ml of either test drug or saline intrathecally, depending on their group assignment. Transdermal patches, either placebo or nitroglycerin, were applied at the thorax, in a nonanesthetized area, 20–30 min after spinal puncture. Pinprick tests were administered at 5, 10, and 15 min after injection. Blood pressure, heart rate, and oxymeglobin saturation were monitored continuously during surgery. Postoperative assessments included pain scores, adverse effects, and duration of motor block. Pain was assessed at the time of first rescue analgesic and 24 h after the spinal puncture by a second anesthesiologist blinded to study drug preparations.

Results showed that intrathecal sufentanil resulted in 5.4 h of analgesia after spinal puncture, and that 5 mg of transdermal nitroglycerin treatment produced no postoperative analgesia. However, the combination of intrathecal sufentanil and a 5 mg transdermal nitroglycerin patch resulted in 13 h of postoperative analgesia after arthroscopy/menisectomy procedures, more than a twofold increase. The need for additional analgesic medications in the first 24 h after surgery was also significantly lower in the sufentanil/nitroglycerin group. Despite the observed enhancement of the analgesic effects of intrathecal sufentanil by topical nitroglycerin, the safety of this approach needs further confirmation with...
dose–response studies and careful observation for potential adverse effects.

- Improving Outcomes after Breast Biopsy by the Use of Benzodiazepine Premedication. van Vlymen et al. (page 740)

Women scheduled for breast biopsies often report experiencing high levels of anxiety before the procedures. In their prospective, randomized, double-blind, and controlled study, van Vlymen et al. sought to determine whether premedication with either midazolam or diazepam emulsion would lessen women’s levels of anxiety and increase their comfort levels during needle localization and breast biopsy. A pilot study conducted before the randomized trial had found that, although most women were satisfied with their intraoperative and postsurgical care during needle localization and breast biopsy, 34% complained of moderate to severe discomfort during needle localization.

Accordingly, the team recruited 90 women, ASA status I–III, and randomly assigned them to one of three premedication groups. The first dose of premedication was given 5 min before women were transferred from the day surgery unit to the radiology department, where needle localization was performed. The second dose was administered 5–10 min before patients entered the operating room (OR). Patients and the anesthesiologist observer were blinded as to drug preparation. Patients in the placebo group received 2.0 ml intravenous saline in two separate doses; patients in the midazolam group received 1.0 mg and then 2.0 mg intravenous doses; and patients in the diazepam emulsion group were administered 2.0 and 5.0 mg/ml intravenous. All women assessed their anxiety levels (using a 100-mm visual analogue scale) before the needle localization procedure, before moving to the OR and at arrival at the OR.

In all three study groups, a variable-rate infusion of propofol (ranging from 25 to 150 μg·kg⁻¹·min⁻¹) was used for intraoperative sedation. Fentanyl, 25 μg intravenous, was used to minimize pain during anesthetic infiltration. The blinded observer assessed sedation levels using the OAA/S scoring system. Propofol was discontinued when the incision was closed, and patients were returned to a step-down area in the day surgery unit.

Visual analog scale anxiety scores were significantly lower for the women receiving midazolam and diazepam emulsion at arrival in the OR. The mean propofol infusion rate was also significantly lower in both premedication groups. More than 90% of patients receiving diazepam emulsion premedication considered that premedication to be beneficial before needle localization and 97% said they would choose the same premedication again for a similar procedure. In the midazolam group, 74% of women considered the premedication to be helpful and 83% would choose it again. Only 38% of patients in the saline group found their premedication to be helpful, and only 55% would choose it in the future. Only 20% of the patients receiving midazolam and 6% of women receiving diazepam emulsion experienced moderate to severe discomfort during needle localization, compared with 70% of patients who reported such discomfort in the saline (control) group. Two patients in the control group experienced vasovagal symptoms during needle localization, but none of the women receiving benzodiazepines had any such reactions. Additionally, there were no differences in discharge times in patients who received benzodiazepine premedication. Diazepam emulsion may offer cost advantages over midazolam, and the reduction in anxiety levels and high satisfaction levels attest to the effectiveness of either premedication in this setting.

- Effects of Propofol and Ketamine on Airway Reactivity Examined in Sheep Model. Brown et al. (page 822)

In patients with asthma, tracheal intubation increases the risk of development of severe bronchospasm. The most effective agent for preventing bronchospasm in such patients remains a subject of controversy. Propofol has been shown to decrease the incidence of wheezing compared to thiopental in healthy and asthmatic patients who were tracheally intubated. Ketamine has also been shown to be effective in preventing and reversing wheezing in asthmatic patients requiring anesthesia and intubation. Brown et al. evaluated the ability of propofol and ketamine to attenuate direct and reflex-induced airway constriction in the sheep model.

Eight sheep were anesthetized with pentobarbital, paralyzed, and ventilated. The team opened the left thorax at the fifth intercostal space and ligated the esophageal and thoracic tracheal branches of the bronchoesophageal artery. The bronchial branch was cannulated and perfused. After a 30-min recovery period, baseline airways resistance (Raw) was measured. Baseline measurements were also determined after vagal nerve stimulation and metacholine challenge. In random order, propofol, ketamine, and thiopental, at clinically relevant
3 concentrations of 5 mg/ml, were infused into the BA at a rate of 0.06, 0.2, and 0.6 ml/min. After 10 min of infusion at each rate, the Raw was measured prechallenge and during constriction by vagal nerve stimulation and metacholine infusion. Airway measurements were repeated after each infusion rate, and sheep were allowed to recover for 30–60 min between the final infusion of one drug and the first infusion of the next.

Infusion of propofol and ketamine into the BA caused a dose-dependent attenuation of the vagal nerve stimulation-induced bronchoconstriction down to 26 ± 11% and 8 ± 2% of maximum. In addition, propofol caused a significant decrease in the metacholine-induced bronchoconstriction, to 43 ± 27% of maximum at the highest concentration. Systemic blood pressure was not affected by any of the drugs, supporting the notion that the decrease in airway responses was local to the airways and not caused by changes in circulating catecholamines. At concentrations similar to those achieved in clinical practice, ketamine and propofol inhibit bronchoconstriction primarily by reducing activity in nerves that supply the airways.

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