Advantages to Combining Low-dose Ketamine and Nitroglycerin with Morphine for Cancer Pain Management? Lauretti et al. (page 1528)

The management of chronic cancer pain is complicated by opioid analgesic tolerance, leading to decreased analgesic response when a fixed opioid dose is repetitively administered. Lauretti et al. designed an unblinded pilot study to evaluate the role of oral ketamine and transdermal nitroglycerin as adjuvants to oral morphine in cancer pain therapy. Sixty patients suffering from cancer pain, all of whom were taking oral amitriptyline, 50 mg, at bedtime, were enrolled in the study.

All patients in the study had free access to oral morphine individually adjusted to a maximal oral dose of 80–90 mg/day. When they complained of pain (VAS of 4 or greater despite taking the maximum dose), patients were assigned to one of four groups to receive the additional test drugs. The control group (CG) received additional oral morphine (10 mg at 12-h intervals), and the dipyridamole group (DG) received 500 mg of the nonsteroidal antiinflammatory drug at 6-hour intervals. The ketamine group (KG) received oral ketamine, 0.5 mg/kg, at 12-hour intervals, and the nitroglycerin group (NG) received a 5 mg transdermal nitroglycerin patch daily. Patients' daily consumption of morphine and their VAS scores were recorded on days 1, 5, 10, 15, 20, and 30 after introduction of the test drug. Patients in the KG maintained analgesic effects during the 30-day observation period without the need for morphine dose escalation. After day 20, patients in the KG experienced an analgesic effect, and after day 30, both the KG and NG patients consumed less morphine than patients in either the DG or CG. Patients in the KG and NG also had fewer complaints of sleepiness, less nausea and vomiting, and a delayed necessity for invasive procedures, such as spinal pain control therapy. Results from this pilot study suggest that oral ketamine and transdermal nitroglycerin might be effective coadjuvant analgesics. Through their opioid tolerance sparing function, these drugs might decrease the adverse effects that stem from receiving high doses of opioids administered via patient-controlled devices to control postoperative nausea and vomiting (PONV). Patients were given instructions on using the patient-controlled analgesia machine during the preoperative period. They received a standardized general anesthetic, comprised of premedication with midazolam, 1–2 mg, induction with fentanyl, 2–5 μg/kg, thiopental, 3–5 mg/kg, and maintenance of anesthesia with fentanyl, isoflurane, and N2O. Patients experiencing significant nausea (5 or greater on a 10-point verbal rating score) or vomiting and asking for an antiemetic within 1 hour of entry to the recovery room were enrolled in the study. They were randomized to receive either placebo, propofol, 20 mg, or propofol, 40 mg. Study drugs had been prepared by the pharmacy in 50-mL glass syringes in equal volume, so investigators and patients were blinded as to which drug was being administered. Rescue antiemetic (ondansetron, 4 mg) was administered at the patient's request or if the patient had two or more episodes of emesis in a 30-minute period. At 15, 30, 60, 90, and 120 min after initiating treatment, severity of nausea VRS, episodes of vomiting or retching, antiemetic use if any, respiratory rate, and hemodynamics were assessed. A lock-out interval of 5 min between doses was used, and study drugs were discontinued after 2 h.

Significantly more patients in the placebo group experienced vomiting and received rescue antiemetic than did those in the propofol groups. Most of the patients receiving propofol reported satisfaction with their treatment as opposed to only 43% in the placebo group reporting satisfaction with treatment. Two patients receiving propofol, 40 mg, experienced oversedation; there was no difference in efficacy between 20 and 40 mg, the authors recommend a 20-mg demand dose of propofol.

This is the first reported study in which propofol is used as an antiemetic delivered by a patient-controlled device. Although the study demonstrated that this approach is feasible, other studies are needed to compare its cost–benefit ratio with other delivery methods, such as small-dose continuous infusion or nurse-administered propofol.

Investigation of Subhypnotic Doses of Propofol for Curb Postoperative Nausea and Vomiting. Gan et al. (page 1564)

From a pool of 200 patients slated for day surgery, 69 patients met entry criteria for a study by Gan et al. designed to test the efficacy of small doses of propofol administered via patient-controlled devices to control postoperative nausea and vomiting (PONV). Patients were given instructions on using the patient-controlled analgesia machine during the preoperative period. They received a standardized general anesthetic, comprised of premedication with midazolam, 1–2 mg, induction with fentanyl, 2–5 μg/kg, thiopental, 3–5 mg/kg, and maintenance of anesthesia with fentanyl, isoflurane, and N2O. Patients experiencing significant nausea (5 or greater on a 10-point verbal rating score) or vomiting and asking for an antiemetic within 1 h of entry to the recovery room were enrolled in the study. They were randomized to receive either placebo, propofol, 20 mg, or propofol, 40 mg. Study drugs had been prepared by the pharmacy in 50-mL glass syringes in equal volume, so investigators and patients were blinded as to which drug was being administered. Rescue antiemetic (ondansetron, 4 mg) was administered at the patient's request or if the patient had two or more episodes of emesis in a 30-min period. At 15, 30, 60, 90, and 120 min after initiating treatment, severity of nausea VRS, episodes of vomiting or retching, antiemetic use if any, respiratory rate, and hemodynamics were assessed. A lock-out interval of 5 min between doses was used, and study drugs were discontinued after 2 h.

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Effects of Antiinflammatory Pretreatments on Acid- and Bacteria-induced Lung Injury. Miyazaki et al. (page 1650).

Using New Zealand White rabbits, Miyazaki et al. conducted a series of experiments to determine the possible
protective effects of pretreatment with two antiinflammatory agents on subsequent induced lung injuries. Pretreatments consisted of either intravenous pentoxifylline (20 mg/kg bolus and 6 mg·kg⁻¹·h⁻¹); anti-TNF-α antiserum (1 ml) or normal intravenous saline solution. In the first set of experiments, hydrochloric acid was instilled into the animals' right lungs after pretreatment. The animals were mechanically ventilated for 8 h and then killed, and their lungs were excised for examination. Compared with animals receiving no pretreatment, those who received either pentoxifylline or anti-TNF-α antiserum sustained less acid-induced lung injury, as evidenced by less edema and more favorable arterial oxygen tension levels.

In the second set of experiments, designed to mimic clinical scenarios, Pseudomonas aeruginosa bacteria were instilled 24 h after the acid-induced lung injury. In this sequence, pentoxifylline was superior to anti-TNF-α antiserum in blocking injury to the lung. The pentoxifylline pretreatment significantly improved the measurements of left lung edema and epithelial and endothelial permeability. There was also a trend toward improved oxygenation in the pentoxifylline-pretreated animals. The authors conjecture that the mechanism of TNF-α blockade may have important effects on host defense and that increases in interleukin-8 may contribute to lung injury. Bacterial lung infections are common in patients who have experienced acid aspiration or other lung injuries, so it is important to assess potential therapies in terms of their effects on subsequent bacterial infections.

4-Chloro-m-cresol as a Trigger of Malignant Hyperthermia in Susceptible Swine. Wappler et al. (page 1733), Iaizzo et al. (page 1723)

Used as preservatives in numerous commercial drug preparations (including insulin, heparin, and succinylcholine), chlorocresol derivatives have been shown to induce myoplasmic Ca²⁺ release. The most potent form is 4-chloro-m-cresol (4-Cmc), shown to specifically activate the skeletal muscle ryanodine receptors, thus eliciting muscle contractures in muscles of patients susceptible to malignant hyperthermia. Two studies in this issue (both with in vivo and in vitro components) investigate the ability of 4-Cmc to trigger malignant hyperthermia (MH) in both in swine.

Wappler et al. anesthetized six MH-susceptible Pietrain and six MH normal Hampshire swine, intubated them, and initiated mechanical ventilation, adjusting to maintain PaCO₂ at 40 ± 2 mmHg during the procedures. They obtained muscle specimens from the pigs' hind limbs for separate in vitro experiments. All animals were maintained normothermic at 37.0 ± 0.2°C during all surgical procedures. After baseline control measurements and removal of muscle specimens from the pigs' hind limbs, cumulative administration of 4-Cmc began. Intravenous dosages started at 3 mg/kg and were increased to 6, 12, 24, and 48 mg/kg at 20-min intervals. A PaCO₂ more than 70 mmHg, a pH of less than 7.25, and an increase in temperature of 2°C or more were indications of MH; once this occurred, additional doses of 4-Cmc were stopped, and intravenous dantrolene, 3.5 mg/kg was given to counteract the episode. All the MH-susceptible swine developed MH after administration of 12 or 24 mg/kg Cmc, and all were treated successfully with dantrolene. None of the MH normal swine developed signs of MH. After receiving 4-Cmc in a concentration of 48 mg/kg, all MH normal swine died because of ventricular fibrillation. In vitro contracture tests with 4-Cmc in concentrations of 75 and 200 μM demonstrated marked contractures in skeletal muscles from MH-susceptible swine but only small contractures in normal control specimens.

Malignant hyperthermia-susceptible swine were also used by Iaizzo et al. in their investigations of the in vivo effects of 4-Cmc. The animals were anesthetized, intubated, and mechanically ventilated, and their esophageal temperatures maintained slightly higher than the animals in the Wappler group studies: 38.2 ± 0.6°C. After collection of baseline measurements, the animals were divided into two groups to receive different doses of 4-Cmc intravenously. The low-dose group received boluses of 0.14, 0.14, 0.28, 0.57, 1.14, 2.27, and 4.54 mg/kg, whereas the high-dose group received boluses of 1.14, 2.27, 4.54, and 9.08, with a final high dose of 18.18 administered to one animal. In addition to arterial blood PaO₂, PaCO₂, pH, K⁺, Na⁺, HCO₃⁻, and hematocrit readings, the group determined plasma levels of 4-Cmc using liquid chromatography. Percent plasma hemolysis was also measured.

Although transient cardiovascular reactions such as tachycardia and hypotension were observed after low doses of 4-Cmc, these concentrations did not trigger MH episodes. All animals administered higher doses of 4-Cmc elicited fulminating episodes of MH that were fatal when equivalent cumulative concentrations were more than 1,500 μmol. The investigators found that plasma levels of 4-Cmc rapidly decreased, and hemolysis was detected after 4-Cmc administration of concentrations more than 200 μmol.

In vitro contracture testing was performed on intact fiber bundles obtained from rectus abdominal muscles of
MH-susceptible and MH normal swine. Muscle bundles were exposed to increasing doses of 4-CmC after halothane and caffeine contracture testing. Muscle from susceptible animals elicited contractures more than 200 mg at 50 μmol bath concentrations of 4-CmC, but normal muscle fiber did not produce such contractures until the bath concentrations were more than 800 μmol.

Both studies concluded that 4-CmC is a trigger of MH in susceptible swine, but only in concentrations much higher (150-fold) than those likely encountered in clinical situations for humans. Although it is unclear whether 4-CmC poses any danger to humans susceptible to MH, Wappler et al. suggest that the preservative might be useful as a specific test agent for diagnosis of MH susceptibility.

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