Org 25969: A Safer Way to Reverse Neuromuscular Block? Gijsenbergh et al. (page 695)

Gijsenbergh et al. designed a phase 1 safety and efficacy trial to investigate the use of Org 25969, a modified γ-cyclodextrin that encapsulates rocuronium bromide, to reverse the effects of the neuromuscular blocking agent.

The team recruited 19 healthy male volunteers for part 1 of the trial, during which either Org 25969 or placebo was administered to volunteers during one of three treatment periods each. Subjects’ well-being was assessed before administration of Org 25969 and at regular intervals postdose, up to 24 h. The physician involved with safety assessments was blinded to treatments received by the volunteers.

In part 2 of the trial, 10 more subjects received general anesthesia on two occasions. Three minutes after rocuronium administration, in randomized order, volunteers received either Org 25969 or placebo. Assessment of adverse events began after volunteers recovered from anesthesia. Adverse events were classified according to intensity: mild (no interference with normal function), moderate (no significant interference with normal function) or severe (significant interference with normal function). Blood pressure, heart rate, oxygen saturation, and electrocardiograms were assessed as well. In addition, venous blood samples for determination of Org 25969 plasma concentrations were taken at predetermined intervals in both parts 1 and 2 of the study.

All 29 subjects completed the study. One subject in part 1 discontinued his participation after the second treatment period due to an unrelated cardiac event. Other adverse events included taste perversion (one event lasting 2 min, another for 43 min); dry mouth; paresthesia (one event lasting 7 days); and muscular contractions for a 12-h period (in part 2 of the study). When administered as a single intravenous bolus at doses up to 8.9 mg/kg, Org 25969 was well tolerated. Because of this study’s small sample size and isolated out-of-normal-range electrocardiogram values, the safety of this drug must be confirmed in other investigations. In two subjects given 8 mg/kg Org 25969 during a profound neuromuscular blockade, the train-of-four ratio returned to 0.9 approximately 1 min after administration of the reversal agent. During a profound neuromuscular block, the speed of recovery with Org 25969 compared to administration of neostigmine. Further investigation may help reveal variability of recovery times.

Countering Hypotension During Spinal Anesthesia for Cesarean Section. Ngan Kee et al. (page 744)

Hypotension during spinal anesthesia for cesarean section remains a common clinical problem, and is associated with maternal nausea and vomiting as well as fetal acidosis. Ngan Kee et al. recruited 112 women with full-term singleton pregnancies who were scheduled for elective cesarean section under spinal anesthesia. After baseline maternal and fetal hemodynamic monitoring, spinal anesthesia was induced. The women were randomly assigned to one of two groups. In group 1, cohydration using a rapid crystalloid infusion was instituted at the start of intrathecal injection and continued to a maximum until uterine incision. In group 0, the infusion was continued at a minimal rate to maintain vein patency. All participants also received an intravenous infusion of 100 μg/min phenylephrine. Infusions began immediately after spinal injection and were titrated to maintain systolic blood pressure near baseline values until uterine incision.

Six patients were excluded from final analysis. Only one in 53 patients in group 1 experienced hypotension, versus 15 of 53 in group 0. Patients in group 1 had greater values for serial measurements of systolic blood pressure, minimum recorded systolic blood pressure, and minimum recorded heart rate. The total phenylephrine consumption was smaller in group 1 patients. Because of transient episodes of reactive hypertension seen in patients of both groups, the authors recommend caution when applying their technique. Although phenylephrine could be administered by intermittent boluses, use of an infusion is associated with lower incidence, frequency, and magnitude of hypotension, and simply requires frequent monitoring of maternal blood pressure with commensurate review and adjustments of the syringe pump settings. The authors believe that administration of phenylephrine in conjunction with cohydration by rapid crystalloid infusion is a clinically useful technique for avoiding the adverse effects of maternal hypotension associated with spinal anesthesia.
Researchers Target Expression of Voltage-gated Sodium Channel Subtype. Mikami and Yang (page 828)

Several sodium channels contribute to neuronal transmission. A goal of research on sodium channels is to inhibit particular isoforms involved in pathophysiologic processes. NaV1.8 is an isoform of voltage-gated sodium channel implicated in the pathogenesis of inflammatory and neuropathic pain. Mikami and Yang describe a series of experiments in which they blocked production of NaV1.8 utilizing a strategy called RNA interference. They used a lentivirus that is taken up by cells and expresses the small hairpin RNA to block the production of this voltage-gated sodium channel subtype. The virus-induced selective knockdown of NaV1.8 was examined at the protein, messenger RNA, and functional levels using Western blot, immunohistochemistry, reverse transcription polymerase chain reaction, and patch clamp electrophysiology tests.

What they found is that four out of five designed short hairpin RNA sequences for NaV1.8 were effective in knocking down the transcripts for this channel subtype in cultured rat neonatal dorsal root ganglion cells. Whole cell patch clamp recordings confirmed a decrease in the NaV1.8-mediated current density without changes in other biophysical properties. The authors’ findings provide evidence for the potential of short hairpin RNA technology for selective knockdown of NaV1.8 in sensory neurons. The method could open up the possibility of short hairpin RNA-mediated viral vector-based in vivo gene therapy for treatment of chronic neuropathic and inflammatory pain.

Impact of Preoperative Clinic Visits on Operating Room Delays and Cancellations. Ferschl et al. (page 855)

Ferschl et al. conducted a retrospective chart review of all surgical cases requiring anesthesia at their institution for a 6-month period, from July 1 through December 31, 2003. Their aim was to determine the impact of patient visits to an anesthesia preoperative medicine clinic (APMC) on surgery delays and cancellations. At these preoperative clinic visits, patients undergo a history and physical examination by an attending anesthesiologist, as well as any necessary preoperative tests. An anesthetic plan is then formulated.

Surgical cases were divided into two groups: those performed in the eight-room same-day surgery suite and those performed in the 15 general operating rooms. The authors then cross-referenced the surgical cases with a second database containing all patients who had visited the APMC. The study period included 6,254 surgical cases, 3,416 of which were performed in the same-day surgery suite. The overall APMC attendance rate for both same-day and general operating room patients was 43%. Of the same-day surgery cases, 8.4% evaluated in the APMC were cancelled, whereas 16.2% that had not been seen in the APMC were cancelled. After controlling for age, American Society of Anesthesiologists physical status, and type of surgery, the adjusted odds ratio of cancellation for an APMC visitor was 0.36 (95% CI, 0.27–0.47; P < 0.001). Same-day surgical suite delays were reduced an average of 3 min for patients who had been evaluated preoperatively in the clinic.

During the study period, 52% of the 3,108 patients whose cases were performed in the general operating room had been evaluated in the APMC. Overall, a higher percentage of surgery cancellations occurred with patients not evaluated in the APMC, but the authors also found that American Society of Anesthesiologists physical status scores were independently associated with an increased cancellation rate. Fewer cancellations and case delays in patients seen in the APMC suggest that the preoperative clinic played a role in these reductions, and that such preoperative evaluations could have important financial and time management implications.

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