◇ This Month in

ANESTHESIOLOGY

■ Dextromethorphan and Memantine Evaluated for Efficacy in Diabetic Neuropathy and Postherpetic Neuralgia. Sang *et al.* (page 1053)

Using nationwide print advertisements and direct referrals, Sang *et al.* recruited patients with painful diabetic neuropathy (DN) and postherpetic neuralgia (PHN) for a trial of the antitussive dextromethorphan and the antiparkinsonian agent memantine. Inclusion criteria included moderate pain for at least 50% of the day for a minimum of 3 months, or a previously failed trial of tricyclic antidepressants for at least 2 weeks. Exclusion criteria included, among other factors, concurrent use of monoamine oxidase inhibitors, a history of hypersensitivity or intolerance to the two study drugs, or hepatic or renal dysfunction.

Patients were offered enrollment in two sequential randomized placebo control studies. In both, dextromethorphan, memantine, and lorazepam (placebo drug) were dispensed in externally identical capsules. The first trial (Efficacy) compared the analgesic effects of the maximum tolerated dose of the two study drugs to placebo, with all participants receiving all three treatments. The second trial (Dose–Response) was conducted only with patients who had completed at least three weeks of the three drugs in the efficacy trial and who were classified as "responders" (*i.e.*, experiencing at least moderate or better pain relief from one of the active drugs compared with placebo). In essence, the second trial was therefore conducted in an "enriched" sample of patients already known to have responded to treatment. Each treatment consisted of a 7-week titration period to maximum tolerated dose, followed by a 2-week maintenance period. The doses of dextromethorphan ranged from 30 to 100 mg; memantine, from 1.8 to 6.0 mg; and lorazepam, from 0.06 to 0.2 mg. Medications were given four times daily. The targeted maximal doses were 960 mg for dextromethorphan, 58 mg for memantine, and 2 mg for lorazepam. The dose–response trial was comprised of three *N*-methyl-D-aspartate antagonist treatment periods and one active placebo period.

During both trials, a nurse blinded to the study drug called each patient twice a week to elicit reports of any side effects and to titrate the medication. Patient response was judged on a pain intensity scale and by asking patients to assess whether their pain had been relieved. Nineteen of 23 patients with DN and 17 of 21 patients with PHN completed the efficacy trial. Mean reductions in pain intensity for patients with DN were 34% with dextromethorphan and 17% with memantine. Neither response was statistically different from the active control (lorazepam, 16% reduction in pain intensity). Neither of the active drugs statistically reduced pain intensity in PHN patients. However, 13 patients with DN reported moderate or better pain relief with dextromethorphan, while 9 responded to memantine. Five patients with PHN responded to dextromethorphan while only two responded to memantine.

Ten "responding" patients with DN and 7 patients with PHN enrolled in and completed the dose–response phase of the study. The DN patients were all subsequently studied with dextromethorphan, while five of the PHN patients received dextromethorphan, and two received memantine. In DN patients, there was a clear dose-related analgesic effect of dextromethorphan, but the drug had no effect in PHN patients. Neither patient treated with memantine reported any reduction in pain intensity. These results suggest a difference in pain mechanisms and warrant selective approaches, say the authors, when using these low-affinity *N*-methyl-D-aspartate antagonists to treat neuropathic pain.

■ Can Transgenic Recombinant Antithrombin Proteins Maintain Normal Antithrombin Activity during Cardiopulmonary Bypass? Levy *et al.* (page 1095)

Associated with a variety of pathologic conditions, including cardiac surgery, acquired antithrombin (AT) deficiency is more common than hereditary forms of the condition. AT deficiency can lessen the anticoagulant response to heparin, resulting in excessive activation of the hemostatic system during cardiopulmonary bypass (CPB). Consequently, excessive microvascular bleeding may occur and consumption of platelets and coagulation factors increases. Might transgenically produced human AT (rh AT) mediate normal AT activity during CPB, thus optimizing the anticoagulant response to heparin?

For a dose-finding study, Levy *et al.* recruited 36 patients scheduled to undergo elective primary CPB and who had received heparin for up to 12 h or more before surgery. Ten cohorts of three patients each received rh AT over a 30-min period prior to administration of heparin and CPB surgery, in doses ranging from 10 to 200 units/kg, while the remaining six patients received placebo. CPB was performed using moderate hypother-

mia. Blood specimens were drawn before and 1 min after rh AT administration; 5 min after heparin bolus administration; at various points after initiation of CPB; and before and after protamine administration. Standard coagulation and AT activity were measured in all blood specimens. Patients were also tested before and after surgery for antibodies to antithrombin. The authors found that activated clotting times during CPB were significantly greater in patients who received rh AT compared to placebo patients. The rh AT was well tolerated and also decreased levels of fibrin monomer and D-dimer. No appreciable adverse events were observed with any of the rh AT doses used in this study. While the study was not intended to examine blood loss or blood product use, the results suggest that rh AT may be useful in the management of patients with hereditary or acquired AT deficiencies.

■ Serious Complications following Primary Hip or Knee Replacement Assessed over a 10-yr Period. Mantilla *et al.* (page 1140)

Knowledge of the risk of myocardial infarction (MI), pulmonary embolism (PE), deep venous thrombosis (DVT), or death within 30 days of hip or knee arthroplasty could benefit patient decision making and allow focus on strategies that could improve outcomes, maintain Mantilla *et al.* Using the Mayo Clinic's Total Joint Registry and Medical Index, these investigators examined the medical records of 10,244 consecutive patients who had undergone either hip or knee replacement at their institution over a 10-yr period. Each episode of MI, PE, or DVT occurring during the initial 30 days following surgery was categorized according to previously defined criteria, into the highest level of diagnostic certainty—"definite," "probable," and "no event." The end point of death was obtained from documented events in the institutional database and was confirmed using the Social Security Index.

Of the total 10,244 patients who had undergone these elective procedures, 224 had one or more adverse events, for an overall event rate of 2.2%. Most adverse events (MI, PE, and death) increased in frequency the older patients were, particularly if they were 70 yr or older. MI was more frequent in males, and PE was highest in patients undergoing bilateral knee operations. The median times to MI, PE, and death were 1, 4, and 9 days, respectively. The authors conclude that the large volume of cases examined can help practitioners assess current risks of these procedures, although the applicability to other clinical settings is unknown.

■ Neuroprotective Effects of Propofol Assessed in an Awake Rat Model. Gelb *et al.* (page 1183)

While most studies of propofol's effects on cerebral ischemia entail inducing stroke in anesthetized animals, Gelb *et al.* performed experiments using a model that induces stroke in the conscious rat. Four days before experiments commenced, cannulas were surgically implanted into the rats' brains and fixed to their skulls using dental acrylic. After the recovery period, a 30-gauge needle was passed into the striatum *via* the implanted cannula, and 6.0 pmol endothelin was injected over a 2-min period. The investigators then immediately began 4-h intravenous infusions of two different doses of propofol in two groups of rats (25 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} in 7 rats and 15 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} in nine rats). They began an additional infusion of propofol, 25 mg $\cdot$ kg^{-1} $\cdot$ h^{-1}, in five rats beginning 1 h after endothelin injection. Three control groups (of seven, nine, and five rats) received equal volumes of intralipid infusions with timing identical to those in the experimental groups. On the day of endothelin injection and propofol infusion, the animals were monitored continuously for electrocardiogram, arterial blood pressure, and heart rate. Body temperature was monitored using rectal thermometers, and in eight rats, brain temperature was monitored during the propofol and intralipid infusions. All animals were killed 3 days later, and their brains were removed for analysis.

Animals receiving 25 mg $\cdot$ kg^{-1} $\cdot$ h^{-1} propofol (whether started immediately after endothelin injection or delayed by 1 h) had significantly reduced infarct size compared to intralipid controls. The lower dose of propofol (which resulted in sedation but not complete immobility) had no significant effect. To exclude a direct interaction between propofol and endothelin, the investigators used thiobutabarbital-anesthetized rats and examined, *via* videomicroscopy, endothelin-induced cerebral vasoconstriction with or without propofol. Propofol had no effect on the magnitude or time course of the endothelin-induced vasoconstriction. The benefit of propofol seen on infarct size in awake animals became inconsistent and not statistically significant when the dose was reduced to a light sedative concentration.

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