Drug Monitor

Which ED Sedative Is Best?

For cardioversion in the emergency department (ED), which sedative offers fast onset, little cardiopulmonary depression, rapid recovery, and few adverse effects? Researchers from Hospital Clinic, Barcelona, Spain suggest propofol. They tested it against etomidate and midazolam (with or without flumazenil) in a prospective study, and while all four drug regimens were uniformly effective, the combination of quick, sustained recovery and minimal adverse effects gave propofol an advantage.

The researchers randomly assigned 32 hemodynamically stable adults undergoing ED cardioversion to receive either propofol 1.5 mg/kg, etomidate 0.2 mg/kg, midazolam 0.2 mg/kg alone, or midazolam 0.2 mg/kg followed by a 0.5-mg flumazenil bolus after the procedure and a 0.5-mg IV flumazenil perfusion over the next hour. Induction time was short in all patients—though one in the etomidate group (11%), one in the propofol group (11%), and five in the two midazolam groups (36%) needed an extra dose of the respective drug to achieve induction.

The patients who received midazolam alone took the longest to wake up: a median of 21 minutes, compared with nine and a half minutes for etomidate, eight minutes for propofol, and three minutes for midazolam plus flumazenil. Midazolam patients also had significantly longer total recuperation times, with a median of 45 minutes, compared with 14 minutes for etomidate, 10 minutes for propofol, and five minutes for midazolam plus flumazenil. Although the addition of flumazenil to midazolam dramatically shortened awakening and recovery times, all but one patient in this group became resedated after the flumazenil was discontinued, which delayed discharge.

The disadvantage with etomidate was its adverse effects. Four patients in this group exhibited myoclonus, and one had a generalized, intense, seizure-like case. No patients in any of the other groups had this complication, which can interfere with electrocardiogram interpretation.

While noting the small size of their study sample, the researchers concluded that propofol is superior to other sedatives for patients undergoing brief but painful procedures. They call, however, for additional studies before these results are generalized to other patient populations.

Source: *Ann Emerg Med*. 2003;42:767–772.

New Biodefense Tools Under Development

"Needle free" vaccines for anthrax, ricin, and other potential biological weapons may be on the horizon. In January, BioSante Pharmaceuticals (Lincolnshire, IL) was awarded a subcontract from the DynPort Vaccine Company (Frederick, MD) to develop an anthrax vaccine that could be administered through nasal, oral, and alternative transcutaneous routes. This research is in support of the U.S. DoD Joint Vaccine Acquisition Program.

Most vaccines require an adjuvant to produce a sufficient immune response in the recipient, and the only vaccine adjuvant currently approved by the FDA for human use is aluminum hydroxide. BioSante, however, has developed a nanoparticulate-based vaccine adjuvant that's been shown in animal studies to produce a response similar to that of aluminum hydroxide—but at much lower concentrations, thus allowing the vaccine to be administered through alternate routes. It remains to be seen whether this holds true for the new anthrax vaccine under development.

As part of this program, BioSante researchers will continue to explore new methods of drug delivery. "This program," says Stephen M. Simes, president and chief executive officer of BioSante, "is an important step toward the development of novel vaccines to protect against anthrax and takes advantage of BioSante's work in alternative routes of administering vaccines and therapies."

Over the past year, BioSante has entered into Cooperative Research and Development Agreements with the U.S. Army Medical Research Institute of Infectious Disease and the U.S. Naval Medical Research

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Center to develop nanotechnology-based, needle free biodefense vaccines against anthrax, bubonic plague, staphylococcus, ricin, and malaria.

Sources: BioSante Pharmaceuticals, Inc. News Release. January 7, 2004.

BioSante Pharmaceuticals, Inc. News Release. February 3, 2004.

Aspirin Plus Ibuprofen: Safe After MI?

Concerns about aspirin's cardioprotective effects being diminished by concurrent use of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen may be unfounded, say researchers from Yale University, New Haven, CT and Denver Health Medical Center, Denver, CO. Although it's known that ibuprofen competitively inhibits aspirin's binding site on platelets, findings from a large, retrospective database analysis indicate that these pharmacodynamic factors don't have much clinical effect on the risk of death after myocardial infarction (MI).

The researchers analyzed data on 70,316 U.S. patients aged 65 or older who were hospitalized for MI between 1994 and 1996 and were discharged with an aspirin prescription. Of those, 66,739 were prescribed aspirin alone, 844 were prescribed aspirin plus ibuprofen, and 2,733 were prescribed aspirin plus other NSAIDs. After one year, the percentages of patients who had died in each group were similar: 17.5% for aspirin alone, 14% for aspirin plus ibuprofen, and 15.8% for aspirin plus other NSAIDs.

An earlier report that patients with established cardiovascular disease were at increased risk when they took both aspirin and ibuprofen received extensive media attention, the researchers say, and influenced recommendations against prescribing the two drugs together. They note, however, that the sample size of that study was comparatively small, and there was no adjustment for severity of cardiovascular disease. By contrast, their retrospective study included four times as many patients taking aspirin and ibuprofen and adjusted for such measures of severity as shock, ejection fraction, and heart failure.

Source: *BMJ.* 2003;327: 1322–1323.

Doxazosin and Finasteride: A Winning Team

Combination doxazosin and finasteride therapy works better than either drug alone when it comes to treating benign prostatic hyperplasia (BPH), say researchers for the Medical Therapy of Prostatic Symptoms (MTOPS) Research Group. They conducted a long-term, double-blind, placebo-controlled trial in 3,047 men over age 49, comparing the effects of the two drugs—alone and combined—on clinical progression of BPH.

Over a mean follow-up of 4.5 years, the researchers documented 351 primary outcome events—that is, the first occurrence of either an increase in the American Urological Association (AUA) symptom score of at least four points over baseline, acute urinary retention, renal insufficiency, recurrent urinary tract infection, or urinary incontinence. Of those events, 49 (14%) were in the combination group, 85 (24%) were in the doxazosin group, 89 (25%) were in the finasteride group, and 128 (36%) were in the placebo group. Increases in the AUA score comprised the majority of events.

Compared with placebo, combination therapy reduced the risk of overall clinical progression by 66%—which was significantly higher than the risk reduction with doxazosin or finasteride monotherapy (39% and 34%, respectively). In addition, combination therapy improved AUA scores and maximal urinary flow rate better than either drug did alone.

At four years, serum prostate-specific antigen (PSA) levels had increased by a median of 15% in the placebo patients and 13% in the doxazosin patients. By startling contrast, serum PSA levels had dropped by 50% in both the finasteride and combination treatment patients. Similarly, prostate volume in the 1,148 men who were receiving placebo or doxazosin increased by a median of 24%, while the 427 men taking either finasteride or combination therapy had their prostate volume decrease by a median of 19%.

The reduction in prostate volume may have been a salient factor in the reduction in risk of acute urinary retention and the need for invasive therapy, the researchers say. They also point out that increases in AUA scores were clinically significant, since bothersome symptoms are the most common reason for invasive therapy. Most patients in the study considered a four-point increase indicative of a global sense of worsening of their condition. ●

Source: *N Engl J Med.* 2003; 349:2387–2398.