Drug Monitor

Hope for Progesterone in Treating TBI

There are no proven neuroprotective drugs for patients with traumatic brain injury (TBI), but progesterone treatment offers some faint hope. In the phase 2, randomized, double-blind, placebo-controlled Progesterone for Traumatic Brain Injury—Experimental Clinical Treatment (ProTECT) trial, researchers from Emory University and Morehouse School of Medicine, both in Atlanta, GA, found that administering progesterone to adults with TBI appeared to do no harm and may have done some good.

In the study, 77 adults treated at Grady Memorial Hospital in Atlanta, GA for TBI from blunt trauma were randomly assigned to receive intravenous progesterone, and 23 were assigned to placebo. Because health care proxies were required to give consent for patients to participate in the study, there were frequent delays in administering treatment.

Throughout the three-day infusion interval, the progesterone group had a lower increase in mean temperature compared with the placebo group. The researchers stress the importance of this finding because internal release of progesterone is associated with a 1°F increase in core temperature, and it's been suggested that elevated temperatures may have an adverse effect on neurologic outcome.

Seven placebo patients (30%) and 10 progesterone patients (13%) died within 30 days of injury. There was a strong trend toward reduced mortality from neurologic causes in the progesterone group compared to the placebo group, whereas mortality from non–central nervous system causes was similar between the groups.

Among patients with an index Glasgow Coma Scale (GCS) score of 4 to 8 (indicating severe injury), the relative risk of death for progesterone versus placebo treatment was 0.33. But for patients whose index GCS score was between 9 and 12 (indicating moderate injury), a slightly greater proportion of progesterone patients died compared with placebo patients (16.7% versus 14.3%, respectively; relative risk, 1.17).

The researchers suggest that the increased survival among severely injured patients who received progesterone might explain why this group also had longer durations of coma and slightly worse 30-day Glasgow Outcome Scale–Extended and disability rating scores compared with their counterparts who received placebo. By contrast, progesterone treatment was associated with significantly better outcome and disability scores, compared with placebo, in patients who survived moderate injuries.

The exact nature of progesterone's neuroprotective properties in humans is not clear, but several animal studies have shown that the administration of progesterone immediately following TBI reduces cerebral edema, prevents neuronal loss, and improves functional outcome. The ProTECT researchers recommend conducting a larger trial that involves multiple clinical sites, 1:1 randomization, and rapid administration of treatment.

Source: *Ann Emerg Med.* 2007;49(4):391–402. doi:10.1016/j.annemergmed.2006.07.932.

Does Rosiglitazone Weaken Bones?

Women treated with rosiglitazone for type 2 diabetes mellitus may be more vulnerable to fractures than those taking metformin or glyburide. In February, GlaxoSmithKline (Philadelphia, PA), manufacturer of several products containing rosiglitazone, notified health care providers of these findings from the randomized, double-blind, parallel group study known as A Diabetes Outcome and Progression Trial (ADOPT).

ADOPT included 4,360 patients with recently diagnosed type 2 diabetes who received rosiglitazone, metformin, or glyburide monotherapy. After four to six years of follow-up, the efficacy analysis showed a lower cumulative incidence of monotherapy failure with rosiglitazone (15%) than with either metformin (21%) or glyburide (34%).

The increase in fractures associated with rosiglitazone occurred only in women. The majority of fractures occurred in the upper arm, hand, or foot—not the hip or spine, as is common in postmenopausal women with osteoporosis. Based on these findings, an independent safety committee reviewed an interim analysis of data from another ongoing rosiglitazone trial and found consistent results. GlaxoSmithKline recommends that health care providers consider the risk of fracture when making treatment decisions for patients—especially women—with type 2 diabetes.

Sources: GlaxoSmithKline letter. February 2007. http://www.fda.gov/medwatch/safety/2007/Avandia_GSK_Ltr.pdf.

N Engl J Med. 2006;355(23):2427–2443.

The Ups and Downs of Adjunctive Antithyroids

In patients with hyperthyroidism, antithyroid drugs often are used before, during, or after radioiodine treatment to mitigate the risk of posttreatment

hypothyroidism. But the practice is hotly debated—with unanswered questions including: do the detrimental effects outweigh the benefits, does the timing of antithyroid treatment matter, and do the various antithyroid agents differ? To learn more, researchers from University Hospital Basel, Basel, Switzerland; University Hospital Odense, Odense, Denmark; University of Glasgow, Glasgow, Scotland; and Johns Hopkins University School of Medicine, Baltimore, MD conducted a meta-analysis of 14 randomized, controlled trials involving 1,306 patients.

Overall, they found that adjunctive antithyroid therapy significantly increased the risk of radioiodine treatment failure (relative risk, 1.28). At the same time, though, the drugs significantly reduced the risk of developing hypothyroidism up to a year after treatment (relative risk, 0.68).

The effects appeared to be similar for all three antithyroid drugs studied (carbimazole, propylthiouracil, and methimazole), though the researchers note that a few nonrandomized studies have suggested that propylthiouracil may have "more distinct and protracted effects" than the imidazoles. On the basis of these studies, they say, methimazole or carbimazole might be preferable to achieve euthyroidism when planning radioiodine therapy.

Giving antithyroid drugs during or in the week after radioiodine treatment was associated with a higher relative risk of treatment failure and a lower relative risk of hypothyroidism, compared with a pretreatment strategy. The researchers also found a trend toward increased treatment failure in trials that used fixed radioiodine doses, compared with those that adapted dose calculations to iodine uptake, when antithyroid drugs were given before radioiodine.

The researchers note that the quality of reported methods was poor for most of the trials studied. Furthermore, the limited duration of follow-up was problematic given that the incidence of hypothyroidism increases progressively with each posttreatment year. They call for adequately powered, long-term follow-up trials to examine whether longer discontinuation intervals of different antithyroid drugs can lead to better avoidance of hyperthyroidism relapse while minimizing the risk of hypothyroidism.

Source: *BMJ.* 2007;334(7592):514. doi:10.1136/bmj.39114.670150.BE.

Stable CAD: Is Drug Therapy Enough?

Percutaneous coronary intervention (PCI) is commonly used as an initial therapy for stable coronary artery disease (CAD), even though treatment guidelines recommend trying medication, risk factor reduction, and lifestyle changes first. Now, results from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial confirm that the addition of PCI to pharmacologic therapy doesn't improve outcomes.

This five-year, multicenter, randomized trial—which was supported by the VA Cooperative Studies Program, the Canadian Institutes of Health Research, and multiple industry sponsors—included 2,287 patients from 50 U.S. and Canadian centers, including 15 VA facilities. All patients had objective evidence of myocardial ischemia and significant CAD. The researchers randomly assigned 1,149 patients to undergo PCI and optimal medical therapy (OMT) and 1,138 to receive OMT alone. OMT included antiplatelet, antiischemic, and aggressive lipid lowering pharmacotherapy.

The researchers found no significant differences between the two groups in the rates of death from any cause, nonfatal myocardial infarction, stroke, and hospitalizations for acute coronary syndrome. While patients who received PCI and OMT had significantly more relief from angina, those who received OMT alone also experienced substantial relief.

The researchers suggest that part of the explanation for the ineffectiveness of PCI in this setting is that stable atherosclerotic plaques are relatively unlikely to trigger an acute coronary event, even in cases of severe stenosis. They say their findings reinforce assertions that PCI can be deferred safely in patients with stable CAD—provided that they undergo "intensive, multifaceted medical therapy."

Source: *New Engl J Med.* 2007;356(15):1503–1516.

New Antihypertensive Drug Targets Renin

The FDA has approved a novel antihypertensive drug—aliskirin, marketed by Novartis (East Hanover, NJ) as Tekturna—that directly inhibits renin, a key early trigger of high blood pressure. In six placebo-controlled trials involving more than 2,000 patients with mild to moderate hypertension, once-daily aliskirin lowered blood pressure for up to one year.

The drug was effective in all demographic subgroups, although African American patients tended to have smaller blood pressure reductions compared to white or Asian patients. When aliskirin was combined with hydrochlorothiazide, the reductions were even more pronounced.

Adverse effects of aliskirin were usually mild and transient. The most common of these was diarrhea, which was reported by approximately 2% of patients taking the higher of two approved doses (150 mg and 300 mg). As with other drugs that work directly on the renin-angiotensin system, aliskirin is contraindicated in pregnancy. ●

Source: FDA news release. March 6, 2007.