Drug Monitor

HRT and Ovarian Cancer: How Does Dose Affect Risk?

Oral hormone replacement therapy (HRT) is associated with a risk of ovarian cancer in women who have not undergone hysterectomy, but there is "strong evidence" that reducing the daily dose of estrogen from oral HRT can lower the cancer risk. Such were the findings from a study conducted by researchers from the Danish Cancer Society and Rigshospitalet, Copenhagen and Skejby University Hospital, Aarhus, Denmark. They conducted person-to-person interviews with 1,487 nonhysterectomized women—376 of whom had epithelial ovarian cancer and 1,111 of whom were controls.

The risk of ovarian cancer increased with the cumulative oral intake of estrogen, but not with that of the progestogenic component. Duration did not appear to be a significant factor with either.

If a woman is taking HRT only for irregular bleeding, the researchers suggest that treatment with progestogen alone may be preferable. If an estrogen component is required to alleviate menopausal symptoms, the lowest possible daily dose should be used.

Source: *Arch Intern Med*. 2004;164:2253–2259.

Determining Length of Treatment for Major Depression

Longer treatment is the best way to make a substantial impact on patients with depression, say researchers from the Department of Human Services, Melbourne, Australia; the School of Population Health, University of Queensland, Herston, Australia; the Department of Public Health, Erasmus Medical Center, Rotterdam, the Netherlands; and the Clinical Research Unit for Anxiety and Depression, University of New South Wales, Sydney, Australia. They created "what if" scenarios to compare the effects of no treatment, current treatment, and optimal treatment strategies with cognitive behavioral therapy or antidepressant drug treatment.

Based on a meta-analysis of data on Australian adults with major depression, they estimate that current episodic treatment averts 9% and optimal episodic treatment with cognitive behavioral therapy could avert 28% of the disease burden. During the five years following a major depressive episode, they say, current episodic treatment would avert 13% of Disability-Adjusted Life Years. By contrast, despite assuming adherence rates of only 60%, maintenance drug treatment could avert 50% and maintenance cognitive behavioral therapy could avert 52% of depression occurring within the five years following an episode of major depression.

The researchers say long-term maintenance treatment prevents relapses, and any relapses that occur are treated from the start rather than after a lag time. They point out that people with depression tend to have multiple episodes over a lifetime and are prone to relapses shortly after an index episode. Thus, they say, there are convincing arguments for treating all depression as a chronic disorder—not just depression with recurrent or very severe episodes.

Source: *Arch Gen Psychiatry*. 2004;61:1097–1103.

Comparing Effects of Daily and Twice Weekly Simvastatin

Twice-weekly simvastatin is as effective, and perhaps safer, than daily doses, say researchers from the Southern Arizona VA Health Care System, Tucson. They switched 31 patients from simvastatin 10 or 20 mg daily to 40 or 80 mg weekly for 12 weeks. They then compared lipid profiles at enrollment, week six, and week 12.

Two thirds of the patients, most of whom had low-density lipoprotein cholesterol (LDL-C) goal levels of less than 160 or 130 mg/dL, maintained their LDL-C goal levels after 12 weeks. Three patients reported not adhering to the regimen. A slight majority of patients found the twice weekly regimen as easy or easier

to follow than the daily regimen.

If 83% of the patients at their facility could be converted to the twice-weekly schedule, the researchers hypothesize, the estimated annual cost savings would be $22,000 per 1,000 patients. A larger clinical trial is needed, they add, to further establish the efficacy and safety of this approach.

Source: *Ann Pharmacother*. 2004;38:1789–1793.

New Drug for Lung Cancer

The FDA has approved erlotinib—marketed as Tarceva by OSI Pharmaceuticals Inc, Melville, NY—as a single-agent treatment for locally advanced or metastatic non-small cell lung cancer that has continued to progress despite other treatments. In a study comparing erlotinib to placebo in 731 patients, median survival was 6.7 months for patients taking the drug, versus 4.7 for patients taking placebo.

The drug blocks signals that stimulate growth in cancer cells by inhibiting an enzyme associated with epidermal growth factor receptor (EGFR). Among the approximately 55% of patients who had high levels of EGFR, the effect of erlotinib on survival was much greater than it was among those with low EGFR levels. Common adverse effects included diarrhea, rash, nausea, and vomiting.

Source: FDA News Release, November 19, 2004.

Lisinopril and Tizanidine: Potential for Trouble

According to physicians from Taipei Veterans General Hospital in Taipei, Taiwan, an interaction between lisinopril and tizanidine may have caused "dramatic hypotension" in their patient.

A 48-year-old woman was admitted to the hospital with cerebral hemorrhage, a Glasgow coma scale score of 4, and a decerebrate posture. Since her blood pressure was fairly high at 160/100 mm Hg, she was given antihypertensive agents, including lisinopril 10 mg daily and labetalol 200 mg twice daily. Her blood pressure went down to 135/85 mm Hg and, five days after stroke onset, she regained consciousness. After three weeks, treatment with tizanidine 2 mg was initiated to improve the decerebrate rigidity. Within two hours after the initial dose, her blood pressure plummeted to 66/42 mm Hg.

The physicians found neither a new focal deficit nor a worsened systemic infection. They initiated dopamine to boost blood pressure and withdrew tizanidine and the antihypertensive drugs. Within five hours, her blood pressure rose to 120/50 mm Hg. Dopamine was stopped 20 hours later. Labetolol, amlodipine, nimodipine, and tizanidine were resumed successively 42 hours later when her blood pressure reached 152/85 but did not produce similar problems.

The authors note that tizanidine is an alpha-2 adrenergic agonist much like clonidine, but with less severe adverse effects. Since clonidine can depress blood pressure through volume depletion and an angiotensin converting enzyme inhibitor such as lisinopril may further compromise the renin-angiotensin system, they suggest that tizanidine in combination with lisinopril may provoke the same response.

Source: *Ann Pharmacother*. 2004;38:1840–1843.

Rosiglitazone to Prevent Restenosis

Rosiglitazone significantly reduces restenosis after coronary stent implantation in patients with type 2 diabetes, according to a study by researchers from the schools of medicine at Yonsei University, Seoul, and Pochon CHA University, Sungnam, Kyonggi-do, Korea.

Of 83 patients, 45 with 55 lesions were assigned to the control group and 38 with 51 lesions were assigned to the rosiglitazone treatment group. In the treatment and control groups, respectively, restenosis occurred nine times (in 18% of the lesions) versus 21 times (in 38% of the lesions). The researchers attribute the improved outcomes in part to rosiglitazone's anti-inflammatory properties. The antirestenosis effect is likely to be independent of the known hypoglycemic action of the drug, they say.

Both groups of patients had undergone the maximum treatments for reducing cardiovascular risks—including angiotensin converting enzyme inhibitor, antiplatelet, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, and diet or exercise therapy. As a result, patients in both groups showed significant improvements in fasting plasma glucose levels, glycosylated hemoglobin levels, total cholesterol concentrations, and blood pressure levels. The two groups had similar characteristics, except for the use of rosiglitazone.

The researchers also found that high-sensitivity C-reactive protein concentrations, markers of systemic inflammation, were substantially improved in the rosiglitazone group, compared with the control group. Recent studies, they note, have shown that the inflammatory response plays an important role not

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only in atherosclerosis but also in restenosis after stent implantation.

Source: *Diabetes Care*. 2004;27:2654–2660.

DHEA to Treat Middle-Age Spread?

Can the adrenal hormone dehydroepiandrosterone (DHEA) fight the expanding middle of middle age? According to researchers from Washington University School of Medicine, St. Louis, MO, the marked decline of DHEA after age 25 is a contributor to increased abdominal girth, so replacing it might be a secret weapon in the battle of the bulge.

In this study, 56 patients aged 65 to 71 were randomly assigned to receive DHEA 50 mg daily or placebo for six months. On average, the participants were overweight.

In the DHEA replacement group, visceral fat was reduced, on average, by 10.2% in women and 7.4% in men. Both men and women lost an average of 6% in abdominal subcutaneous fat. While glucose levels were unchanged, insulin levels improved with oral glucose tolerance tests showing significant reductions in areas under the curve after six months of DHEA replacement therapy. The improvement in insulin action was reflected in a significant increase in the insulin sensitivity index.

The replacement treatment raised participants' serum levels of the sulfated form of DHEA into the young normal range. It significantly increased testosterone concentration in the women, though not in the men. Estradiol concentration rose significantly in both male and female participants. The authors note that DHEA slightly but significantly boosted levels of insulin-like growth factor 1, which also reduces abdominal fat. ●

Source: *JAMA*. 2004;292: 2243–2248.