

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CONTENTS

CLINICAL PRACTICE

- Pain Relief During Labor
- Efficacy of Oral Contraceptives in Overweight Women
- C-Reactive Protein Predicts Drug Response in RA
- Britain Issues Guide on Lung Cancer Diagnosis & Treatment

NEW DRUGS & INDICATIONS

- Desmoteplase Ameliorates Stroke and Widens Therapeutic Window

DRUG SAFETY

- Aspirin-PPI Combination Better than Clopidogrel to Prevent GI Bleeds
- Menopausal Hormone Therapy Increases the Risk of Urinary Incontinence

DRUG EVALUATION

- Recombinant Activated Factor VII Stops the Bleeding in Intracerebral Hemorrhage
- Are Benefits of Influenza Vaccine in Elderly Overstated?
- Low-Molecular-Weight Heparin Improves MI Outcome
- Imatinib Produces Regression of AIDS-Related KS Lesions

PHARMACOGENOMICS

- Mutations in the EGFR in Lung Cancer

CLINICAL PRACTICE

Pain Relief During Labor

Pain associated with childbirth is one of the most intense experiences a woman will endure in her lifetime. There are nearly four million births in the U.S. each year and about 60% of women giving birth receive epidural analgesia. The others are frequently advised by their physicians to delay the common pain treatment for fear that it will interfere with contractions and lead to a Caesarian section.

In a recent issue of *The New England Journal of Medicine* [2005;352:655-65], researchers report the results of a 750-woman randomized controlled trial in which intrathecal administration of an opioid at the first request for pain relief during labor was compared with parenteral administration of opioid analgesia at the first request for pain relief with deferral of regional anesthesia. No significant differences were observed between the two groups in the rates of caesarian delivery and vaginal delivery requiring instruments. Indeed, progression of labor was more rapid in the group randomly assigned to early regional analgesia.

A related editorial emphasizes the importance of the study, noting that “the common belief in many maternity units that a laboring woman is ‘not ready yet’ for epidural analgesia forces women to endure hours of extra pain, often while they receive less-than-adequate alternative methods of pain relief, such as systemic narcotics, with a concomitant increase in side effects for both themselves and their newborns” [*Ibid*, 718-20].

Efficacy of Oral Contraceptives in Overweight Women

Despite the demonstrated efficacy of oral contraceptives, concerns about risk factors for unwanted pregnancies exist. In clinical trials of the contraceptive implant *Norplant*, the failure rate was substantially higher in women who weighed 70 kg or more than in women who weighed less than 50 kg. In the same vein, clinical trials of a transdermal contraceptive patch showed higher failure rates in women who weighed 90 kg or more.

Researchers have recently reported the results of a study to evaluate the relationship between body weight or body mass index (BMI) and failure rate of oral contraceptives. The population-based case-control study enrolled women with a positive pregnancy test who had filled a prescription for an oral contracep-

(Continued on Supplement page 2)

Drug Therapy Topics Supplement

A Drug Information Center / School of Pharmacy publication.
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CLINICAL PRACTICE (continued)

Oral Contraceptive Efficacy in Overweight Women (continued)

tive within the past three months. These women were age-matched to controls who filled a prescription for an OC but did not have a positive pregnancy test [*Obstet Gynecol* 2005;105:46-52].

The overall rate of pregnancy in oral contraceptive users was 2.2 per 100 women-years. Pregnancy was more common in women who were black, married, smokers, those with lower educational levels, and those with lower family incomes. After controlling for confounding factors, there was a 60% increase in pregnancy risk for those women in the highest quartile of BMI (greater than or equal to 27.3) than in those in the lower three quartiles.

The authors conclude that being overweight may increase the risk of contraceptive failure. They estimate that such a reduction in efficacy would result in two to four pregnancies per 100 women-years of use among overweight women, but point out that this reduced efficacy is still higher than for some other forms of contraception. An explanation for the observation is a body-weight-associated increase in basal metabolic rate and in clearance of medication. Prudence suggests that overweight women avoid low-dose combination oral contraceptives or use them along with a condom [*Prescriber's Letter* 2005;21:210212].

C-Reactive Protein Predicts Drug Response in Rheumatoid Arthritis

The proposition that elevated levels of C-reactive protein (CRP) increase the risk of coronary artery disease is supported by persuasive evidence. Now, researchers suggest that specific patterns of CRP levels can be used to predict responses to infliximab (*Remicade*) in patients with rheumatoid arthritis (RA). Failure to suppress CRP after two weeks of treatment indicated that a therapeutic response is unlikely at 12 weeks [*Arthritis Rheum* 2005;52:42-48].

The investigators analyzed CRP patterns in 207 patients with resistant RA who began treatment with the anti-TNF monoclonal antibody. After 12 weeks of infliximab therapy, 46% of patients failed to achieve the American College of Rheumatology 20% (ACR20) improvement criteria. These nonresponders were further subdivided into three groups: (1) 12 patients who never achieved a CRP level reduction of at

least 20%; (2) 22 patients with an early reduction of at least 20% that was not sustained at week 12; and (3) 58 patients who did achieve and maintain a CRP reduction of at least 20% despite a failure to achieve ACR20. Patients in the first two groups were switched to etanercept (*Enbrel*), while patients in group 3 continued to take infliximab for an additional 12 weeks.

Among group 3 patients, who in the first 12 weeks had a CRP response to infliximab but not a clinical response, 59% achieved ACR20 improvement by week 24. Among patients who were switched to etanercept—clinical nonresponders who failed to demonstrate a CRP response or sustain a CRP response to infliximab—68% achieved an ACR20 response at week 12, with a CRP response in 63%.

Britain Issues Guidance for Diagnosis and Treatment of Lung Cancer

A news report in the *BMJ* [2005;330:439] notes that the National Institute for Clinical Excellence has published guidelines for achieving earlier diagnosis, greater use of evidence-based treatments, and better coordination of care for patients with lung cancer. Patients with stages I and II non-small-cell lung cancer (NSCLC) that is medically inoperable should be treated using an intensive form of radiotherapy rather

than standard radiotherapy. The guidelines also recommend offering chemotherapy to some patients with stages III and IV NSCLC to improve survival, disease control, and quality of life. The role of newly developed epidermal growth factor receptor inhibitors in the treatment NSCLC has yet to be evaluated in the UK.

NEW DRUGS AND INDICATIONS

Desmoteplase Ameliorates Stroke and Widens Therapeutic Window

Drug therapy for the treatment of acute ischemic stroke is severely limited. Outcome is improved by intravenous thrombolysis with recombinant tissue-type plasminogen activator (rtPA), which is the only drug approved for this condition. The use of rtPA, however, is constrained by the need to administer it within three hours of symptom onset. No significant benefit has been witnessed beyond three hours. Most patients with acute ischemic stroke present after the three-hour time window.

The Desmoteplase in Acute Ischemic Stroke trial (DIAS) evaluated the efficacy of another thrombolytic agent, a recombinant version of a highly fibrin-specific enzyme found in the saliva of the vampire bat. Desmoteplase was developed in Europe; U.S. rights are licensed to Forest Labs. In the study, 47 patients were randomly assigned to receive one of three doses of the thrombolytic agent (25 mg, 37.5 mg, or 50 mg) or placebo within three to nine hours of the onset of acute ischemic stroke. An excessive rate of symptomatic intracranial hemorrhage was observed in this cohort, prompting a consideration of lower doses. The next 57 patients to be studied received one of three per kg doses of desmoteplase (62 µg, 90 µg, or 125 µg) or placebo and demon-

strated a better safety profile [*Stroke* 2005;36:66-73].

Among those patients who received 125 µg/kg body weight, reperfusion rates up to 71.4% were observed, compared with 19.2% among those treated with placebo. Favorable clinical outcomes were documented in 60% of patients treated with 125 µg/kg, compared with 22.2% of placebo-treated patients. Magnetic resonance imaging showed reperfusion in 54.3% of patients treated within three to six hours and in 40.0% of patients treated after six hours. Favorable outcomes were achieved in about half of the patients with reperfusion but in only 25% of the patients without reperfusion. Among those who received desmoteplase 125 µg/kg, favorable 90-day clinical outcomes were achieved in 38.3% of patients treated within three to six hours and in 39.3% of patients treated after six hours.

Thus, DIAS suggests that intravenous desmoteplase given three to nine hours after stroke onset is safe in selected patients and that dose-dependent reperfusion on MRI is correlated with clinical outcomes. Patients who were treated between six and nine hours of stroke onset had a clinical outcome that was as good as those treated within three to six hours. Phase II/III trials are underway to confirm these findings.

DRUG SAFETY

Aspirin-PPI Combination Better than Clopidogrel to Prevent GI Bleeds

Millions of Americans regularly take low-dose aspirin to prevent heart attacks and strokes, but not without risk. Aspirin doubles the chance of upper gastrointestinal bleeding, even at doses as low as 75 mg/day; a history of upper GI bleeding is the most important risk factor for subsequent bleeding in patients taking aspirin. The management of patients who need antiplatelet therapy but are also at risk for GI bleeding is a common clinical dilemma.

Current guidelines recommend clopidogrel (*Plavix*) for patients unable to take aspirin because of previous GI intolerance. An alternative strategy is to administer aspirin with a proton pump inhibitor (PPI). Clinical studies suggest that PPIs reduce the risk of aspirin-induced ulcer bleeding [*N Engl J Med*

2002;346:2033-38]. No prospective trial has assessed whether clopidogrel or aspirin plus a PPI is the safer choice for patients at risk of recurrent bleeding.

A research team has now reported the results of a study that evaluated antiplatelet therapy in 320 patients who had a history of aspirin-induced upper GI bleeding [*Ibid*, 2005;352:238-44]. After eradication of *Helicobacter pylori* and healing, patients were assigned to receive 75 mg clopidogrel once daily or 80 mg aspirin daily plus the PPI esomeprazole at a dose of 20 mg twice daily. The endpoint was recurrent GI bleeding.

Recurrent upper GI bleeding occurred in 13 patients receiving clopidogrel and 1 patient receiving aspirin and esomeprazole. The cumulative incidence of recurrent bleeding during the 12-month study was 8.6% and 0.7%, respectively. The 95% confidence

(Continued on Supplement page 4)

DRUG SAFETY (continued)

Aspirin-PPI vs. Clopidogrel (continued)

interval for the absolute difference was 3.4% to 12.4%. The findings do not support the current recommendation that patients with major GI intolerance of aspirin be given clopidogrel.

A related editorial observes, “It is curious that an agent such as clopidogrel, which does not inhibit cyclooxygenase but targets the ADP receptors of platelets, has gastrointestinal ulcerogenic properties” [*Ibid*, 287-89]. The author suggests that “impairment of healing may be the primary mechanism through which antiplatelet agents cause bleeding,” a possibility that heretofore has not been widely appreciated.

Menopausal Hormone Therapy Increases the Risk of Urinary Incontinence

Menopausal hormone therapy has long been used to treat postmenopausal women and, until recently, was credited with many benefits. Among the purported benefits was improvement in the symptoms of urinary incontinence. To clarify the uncertainties associated with this practice, investigators participating in the landmark Women’s Health Initiative examined urinary incontinence outcomes among the thousands of women who took part in the study. One arm of the

study compared conjugated equine estrogens alone with placebo and the other compared conjugated equine estrogen plus medroxyprogesterone (MPA) with placebo [*JAMA* 2005;293:935-48].

In women who were continent at baseline, estrogen increased the risk of stress incontinence when administered alone (relative risk, 2.15) or combined with MPA (RR, 1.87). Menopausal hormone therapy also increased the risk of mixed and urge incontinence. Women who were incontinent at baseline developed more leakage with estrogen alone and with estrogen plus MPA. Women who received menopausal hormone therapy were more likely to report that urinary incontinence limited their daily activities.

Noting the effects of menopausal hormone therapy after one year of treatment, the authors of the report conclude: “Conjugated equine estrogens with or without progestin should not be prescribed for the prevention or relief of urinary incontinence.” A related editorial concurs, stating that “clinicians should no longer prescribe long-term oral conjugated equine estrogens for treatment of urge, stress, or mixed urinary incontinence in postmenopausal women aged 50 years or older” [*Ibid*, 998-1000].

DRUG EVALUATION

Recombinant Activated Factor VII Stops the Bleeding in Intracerebral Hemorrhage

No specific treatment is available for patients with acute intracerebral hemorrhage, estimated to account for 10 to 15% of all strokes and to have a one-year mortality of 60%. About 40,000 to 50,000 cases of hemorrhagic stroke occur in the U.S. each year. An article in a recent issue of *The New England Journal of Medicine* [2005;352:777-85] offers a new opportunity for targeted therapy for this common cause of neurologic disability and death.

Interventions with hemostatic therapy in the emergency unit might improve outcomes after intracerebral hemorrhage by stopping bleeding and minimizing increases in the volume of the hematoma. Recombinant activated factor VII (rFVIIa) is prescribed under the name *NovoSeven* and is approved to treat bleeding in patients with hemophilia who have antibodies to factor VIII or IX. The clotting factor has also been shown to

reduce bleeding in patients without coagulopathy, at doses that were not associated with a high incidence of thrombotic complications.

The Recombinant Activated Factor VII Intracerebral Hemorrhage Trial, a phase IIb dose-ranging, proof-of-concept study, was designed to determine whether rFVIIa could be administered to reduce hematoma expansion. A total of 399 patients with acute intracerebral hemorrhage in the absence of coagulopathy were assigned to receive one of three doses of the clotting factor (40, 80, or 160 µg per kg body weight) or placebo within four hours after the onset of symptoms.

Hematoma volume increased more in the placebo groups than in the active treatment groups. The

(Continued on Supplement page 5)

rFVIIa Stops the Bleeding in Intracerebral Hemorrhage (continued)

mean increase was 29% in the placebo group, as compared with 11% in the group given the highest dose of rFVIIa. Among placebo-treated patients, mortality was 29% at 90 days, as compared with 18% in the three rFVIIa groups combined, with little difference in the incidence of severe disability. Serious thromboembolic complications—mainly myocardial or cerebral infar-

tion—occurred in 7% of rFVIIa-treated patients, as compared with 2% of those given placebo.

A related editorial opines, “The results of this trial are important but not clinically directive” [*Ibid*, 828-30]. The authors add, “Tempering enthusiasm for rFVIIa as a treatment for intracerebral hemorrhage is the risk of arterial thromboembolic complications.”

Are Benefits of Influenza Vaccine in the Elderly Overestimated?

U.S. policy has long placed elderly people at the top of the priority list for immunization against influenza because they are most likely to be hospitalized or die from the viral infection. Now, however, a controversial analysis of influenza-related mortality over the past 30 years suggests that the vaccine has had less success than presumed at preventing death in those over 65 [*Arch Intern Med* 2005;165:274-80].

The new report focuses on the fact that influenza mortality rates in Americans over 65 have increased despite an increase in vaccination rates in that group, from 15% to 20% in 1980 to 65% in 1991. Previous explanations for this curious observation have pointed to the aging of the elderly population and aggressive strains of influenza that circulated during the 1990s. The new analysis attempted to control for these confounding variables.

The authors of the report say that the vaccine may benefit some elderly people and acknowledge that it may reduce hospitalization. But they point to several studies showing that the vaccine is not as effective in the elderly because their immune systems “senesce.” They also say that their findings strongly suggest that cohort studies reporting a mortality benefit may have wrongly credited the vaccine with preventing deaths because the unvacci-

nated groups had a disproportional number of very sick people.

The reaction to the proposed paradigm shift is sharply mixed. The polarized reaction in part reflects the difficulty of gauging the true impact of influenza. The new analysis measures influenza deaths by examining “excess mortality” that occurs during the flu season. But other respiratory illnesses that circulate during the same season can cause death. Cohort studies also have limitations because they rarely analyze blood to assess whether affected patients really had influenza.

An alternative to targeting the elderly, one that is rapidly gaining advocates, is to vaccinate school-age children, the main “spreaders” of influenza. Proponents of this strategy argue that it could provide a substantial indirect benefit to the elderly [*Science* 2005;307:1026].

In another study, also reported in the *Archives of Internal Medicine* [2005;165:265-72], researchers in the Netherlands show that influenza vaccine remains an effective intervention in people with high-risk medical conditions. In high-risk, primary care adults between 18 and 64 years, influenza vaccine prevented 26% of general practitioner visits, 78% of deaths, and 87% of hospitalizations. A somewhat smaller but nevertheless robust benefit was also observed in high-risk elderly patients.

Low-Molecular-Weight Heparin Improves Outcome after Myocardial Infarction

Early treatment with a low-molecular-weight heparin (LMWH) reduces mortality and reinfarction rates without significantly increasing rates of life-threatening bleeding [*JAMA* 2005;283:427-46]. In the recently reported study, investigators compared reviparin, a LMWH used in Europe and Asia, with placebo in 15,570 patients presenting at medical centers in India and China with ST-segment elevation myocardial infarction (MI) or left bundle branch block; active or sham treatment was administered for seven days.

At 30 days, 13.6% of those assigned to placebo compared with 11.8% of those assigned to reviparin had experienced the primary outcome of death, reinfarction, and stroke. The researchers also observed significant reductions in 30-day mortality and reinfarction and no significant differences in stroke. Further analysis of the outcome of death, reinfarction, strokes, and life-threatening bleeding at 30 days indicates a significant risk reduction (0.87), “suggesting a

(Continued on Supplement page 6)

Low-Molecular-Weight Heparin Improves Outcome after MI (continued)

moderate overall benefit with reviparin when added to conventional therapies.” The researchers estimate that treatment of 1000 patients for one week will prevent 18 deaths or reinfarctions, with an excess of an additional life-threatening bleeding episode (net benefit of 17 events per 1000 patients).

Benefits were still greater when reviparin was initiated early. Administration within two hours of MI onset yielded a hazard ratio of 0.70 compared with a ratio of 1.06 when the LMWH was given eight hours or

longer after MI onset. This suggests that at least some of the benefits of reviparin may be related to improved rates of coronary patency and increased myocardial salvage.

A related editorial says that the study advances the field “by demonstrating that the recommendation for anti-thrombotic therapy can now be made with confidence that the evidence is not built like a house of cards on a series of neutral ‘equivalence trials’ or small outcome trials” [*Ibid*, 489-90].

Imatinib Produces Regression of AIDS-Related KS Lesions

Postulating that imatinib (*Gleevec*), now used to treat chronic myelogenous leukemia and gastrointestinal stromal tumors, might be useful in AIDS-related Kaposi’s sarcoma (KS), researchers administered *Gleevec* 300 mg twice daily for four weeks to 10 patients with AIDS-related KS who had not responded to highly active antiretroviral therapy (HAART) [*J Clin Oncol* 2005;23:982-89]. Tumor measurements showed a partial response in half of the patients, while biopsies of six patients found histological regression in four.

Imatinib is active against both the c-kit receptor and the platelet-derived growth factor receptor (PDGFR).

These receptors are also thought to be involved in the progression of KS. Indeed, immunochemistry showed in three of the biopsies that treatment resulted in reduced activation of PDGFR and extracellular receptor kinase (ERK) pathways. ERK is a downstream effector of PDGFR.

KS is now treated with *Doxil* (liposomal doxorubicin), which has been shown to be effective. Whether or not *Gleevec* provides an advantage over *Doxil* remains to be seen. Clinical efficacy aside, the strength of the report lies in its molecular findings [*Reuters Health*, 28 February 2005].

PHARMACOGENOMICS

Mutations in the Epidermal Growth Factor Receptor in Lung Cancer

Non-small-cell lung cancer (NSCLC) is the leading cause of death from cancer in men and women in the U.S., killing more than one million people each year. Chemotherapy, which is the usual treatment in advanced disease, is only marginally effective. Newer agents—gefitinib (*Iressa*) and erlotinib (*Tarceva*)—which target the epidermal growth factor receptor (EGFR), appear to show promise in metastatic disease. Response rates are 10% to 20% when EGFR inhibitors are used as second- or third-line treatment for advanced disease.

Responsiveness to these drugs, however, seems to be limited to distinct subgroups of patients: women, patients who have never smoked, patients with adenocarcinoma, and Asians. In patients responsive to these medications, the tumor usually contains somatic mutation of the *EGFR* gene. These mutations mediate oncogenic effects and increase the sensitivity of the

tumor to anilinoquinazoline inhibitors of EGFR. Despite the success of these drugs in cases of NSCLC with activating *EGFR* mutations, virtually all cases eventually progress, treatment notwithstanding. The reason for this failure is unknown.

In a recent *Brief Report* in *The New England Journal of Medicine* [2005;352:786-92], researchers describe the case of a patient with EGRF-mutant, gefitinib-responsive advanced NSCLC who had a relapse after two years of complete remission during treatment with gefitinib. According to the authors, “The DNA sequence of the *EGFR* gene in his tumor biopsy specimen at relapse revealed the presence of a second point mutation....” Further studies showed that this second mutation in the tyrosine kinase domain of EGFR led to gefitinib resistance. These findings may lead to more effective drugs for the treatment of NSCLC.