

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

by Milo Gibaldi, Ph.D., School of Pharmacy

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Written by Milo Gibaldi, Ph.D.

Edited by Nelda A. Murri, Pharm. D.

Prepared by Sandra Walston, M.C.

(206) 598-6612/nelda@u.washington.edu

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DRUG EVALUATION

Prompt Interferon Therapy for Acute Hepatitis C Prevents Chronic Infection

Interferon alfa-2b, sold in the U.S. as *Intron A*, is often used to treat chronic hepatitis C, but a new report indicates that it can also prevent chronic infection in patients with acute disease. The results of the pilot study were so impressive that the paper describing them was released on 1 October 2001 by *The New England Journal of Medicine* on its web site, well in advance of its publication on 15 November.

Between 1998 and 2001, the European investigators enrolled 44 patients with early hepatitis C virus infection into a treatment study. The mean age of the patients was 36 years, and 25 of them were women. The group was compared with a similar cohort of 40 untreated patients with acute hepatitis C virus infection who were seen and followed from 1995 to 2000. Patients in the treatment study received 5 million units interferon subcutaneously every day for four weeks, then three times a week for an additional 20 weeks. The average time from infection to onset of treatment was about three months. Hepatitis C virus RNA levels were determined before treatment, after each treatment visit, and 24 weeks after the conclusion of treatment. One patient dropped out of the study, citing side effects. During the course of the study none of the patients treated with interferon progressed to chronic infection. In comparison, 70% of the comparison untreated group did.

In the U.S., chronic hepatitis C virus infection is the leading cause of liver failure requiring transplant and a common cause of cirrhosis. Optimum treatment eradicates the virus only half the time. Halting progression of infection to the chronic phase may be the best way to decrease morbidity and mortality from the virus. An expert hepatologist said he thought the main finding of the new study would be an increase in efforts to catch cases early by screening patients in high-risk groups—health care workers exposed to infected blood, intravenous drug abusers, and children born to infected mothers [*The New York Times on the Web*, 9 October 2001].

Benzodiazepines for Out-of-Hospital Treatment of Status Epilepticus

Status epilepticus requires rapid treatment, and benzodiazepines are the drugs of choice. In recent years, emergency-medical-services (EMS) systems have implemented protocols that allow the intravenous administration of benzodiazepines by paramedics outside of the hospital. The risk and benefits of this strategy, however, have not been studied. Accordingly, researchers conducted a well-

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DRUG EVALUATION (continued)

Benzodiazepines for Out-of-Hospital Status Epilepticus (continued)

controlled trial in adult patients to determine safety and efficacy and to compare lorazepam with diazepam [*N Engl J Med* 2001; 345:631-37]. The investigators determined that status epilepticus had been terminated on arrival at the emergency department in more patients treated with lorazepam (59%) or diazepam (43%) than patients given placebo (21%). After adjustments for

covariates, odds ratios were 4.8 for lorazepam vs. placebo and 2.3 for diazepam vs. placebo. Rates of respiratory or circulatory complications after treatment were 10.6% for lorazepam, 10.3% for diazepam, and 22.5% for placebo. Out-of-hospital treatment by paramedics of status epilepticus in adults is safe and effective. Lorazepam is likely to be more effective than diazepam.

Beta-Blockade Reverses Catabolism After Severe Burns

Increased energy expenditure is associated with severe burns. Protein catabolism is increased, leading to the loss of lean body mass and muscle wasting and increasing the likelihood of delays in rehabilitation, of other complications, and of death. Endogenous catecholamines are primary mediators of the hypermetabolic response to trauma and burns. Because beta-blockade decreases energy expenditure after burns, investigators hypothesized that long-term therapy with propranolol would decrease the rate of muscle-protein catabolism as well [*N Engl J Med* 2001;345:1223-29].

They randomly assigned 24 children with burns over 40% of their body surface area to oral propranolol for at least two weeks or to usual care. The dose of pro-

pranolol was adjusted to decrease resting heart rate by 20% from baseline, to a final average dose of about 1 mg/kg every four hours. Beta-blockade decreased resting energy expenditure. The net muscle-protein balance increased by 82% over baseline values in the propranolol group, but it decreased by 27% in the control group. Fat-free mass was essentially unchanged in the propranolol group, whereas it decreased by an average of 9% in the control group. An editorial noted, "This new therapy should be used cautiously and only in an intensive care unit. Although carefully performed surgery remains the most effective modulator of the hypermetabolic response, new means of reducing catabolism after thermal injury may help make the great constitutional disturbance a thing of the past" [*Ibid*, 1271-72].

HRT Not Helpful for Secondary Prevention of Cerebrovascular Disease

Many observational studies have linked postmenopausal estrogen replacement with a reduced risk of cardiovascular disease, but concern has persisted that these findings may be attributable not to estrogen use but to other differences between users and nonusers. Estrogen therapy may have favorable effects on lipid metabolism, coagulation, and vascular tone, but it also has adverse prothrombotic and proinflammatory effects. Epidemiologic research has also suggested that estrogen might protect against stroke. The Women's Estrogen for Stroke Trial was initiated in 1993 to evaluate estrogen replacement for the secondary prevention of cerebrovascular disease. The results are now available [*N Engl J Med* 2001;345:1243-49].

The study enrolled 664 postmenopausal women (mean age, 71 years), recruited from 21 U.S. hospitals, who had recently had an ischemic stroke or transient

ischemic attack. They were randomly assigned to receive estrogen therapy (estradiol-17 β , 1 mg per day) or placebo for an average of 2.8 years. Women in the estradiol group had a total of 99 strokes or deaths compared with 93 such events in the placebo group. Estrogen therapy did not reduce the risk of death alone or the risk of nonfatal stroke. The women who were assigned to receive estradiol had a higher risk of fatal stroke and their nonfatal strokes resulted in slightly worse neurological and functional deficits. Estrogen therapy should not be prescribed for the secondary prevention of cerebrovascular disease.

Another setback for the manufacturers of *Premarin* and other hormone replacement products is a report concluding that estrogen appears not to retard a decline in cognitive function in postmenopausal women [*Am J Epidemiol* 2001;154:733-39].

NEW DRUGS AND INDICATIONS

New Anticoagulant More Effective Than Enoxaparin After Hip and Knee Surgery

Patients undergoing hip or knee surgery are in the highest risk category for postoperative venous thromboembolism, a condition that could lead to fatal pulmonary embolism if prophylaxis is not provided. Even with current methods of thromboprophylaxis, the incidence of confirmed deep-vein thrombosis is 25% or more.

A recent dose-ranging study of patients undergoing total hip replacement suggested that a once-daily subcutaneous injection of a new synthetic pentasaccharide, fondaparinux, reduces the risk of venous thromboembolism more than does the low-molecular-weight heparin enoxaparin (*Lovenox*) [*N Engl J Med* 2001;344:619-25]. Fondaparinux selectively inhibits activated factor X. Now, two additional studies show that fondaparinux is more effective than enoxaparin in preventing venous thromboembolism after hip and knee surgery.

In one report, researchers randomly assigned 1711 patients undergoing surgery for fracture of the upper femur to receive subcutaneous doses of either fondaparinux 2.5 mg once daily, initiated postoperatively, or enoxaparin 40 mg once daily, initiated preoperatively, for at least five days. The incidence of venous thromboembolism by day 11 after surgery was 8.3% in the fondaparinux group and 19% in the enoxaparin

group. There was no significant difference between the groups in the incidence of death, fatal pulmonary embolism, or clinically important bleeding [*Ibid*, 345:1298-304].

In the other report, investigators randomly assigned 1049 patients undergoing elective major knee surgery to receive either fondaparinux once daily or enoxaparin 30 mg twice daily, with both treatments initiated postoperatively. The incidence of venous thromboembolism was 12.5% in the fondaparinux group and 27.8% in the enoxaparin group. Major bleeding occurred more frequently in the fondaparinux group, but there were no significant differences between the two groups in the incidence of bleeding leading to death or additional surgery or occurring in a critical organ [*Ibid*, 1305-10].

An editorial commenting on the reports observed: "In the operating room, in the intensive care unit, and in patients with renal failure (and in the absence of heparin-induced thrombocytopenia), unfractionated heparin is still the agent of choice, given its short half-life, easy reversibility, and extrarenal metabolism. However, there are clear advantages to the newer agents, and we should use them appropriately, especially in the area of prophylaxis against venous thromboembolism" [*Ibid*, 1340-42].

FDA Approves Second-Generation COX-2 Inhibitor

Pharmacia's second-generation, once-daily oral COX-2 inhibitor, *Bextra* (valdecoxib), has received FDA approval for the treatment of the signs and symptoms of osteoarthritis and rheumatoid arthritis and the treatment of pain associated with menstrual cramping, but not for the treatment of acute pain. In a press release, the company noted that trials in more than 5000 patients have shown that valdecoxib has

comparable efficacy and a better side-effect profile than conventional nonsteroidal anti-inflammatory drugs. According to Pharmacia, *Bextra* may make a commercial impact in keeping with the typical pattern of NSAID use: strong interest in switching from older agents—*Celebrex* and *Vioxx*—to the newest agent in the class [*The Pink Sheet*, 26 November 2001].

Peginterferon Regimen Outperforms Standard Treatment for Chronic Hepatitis C

Interferon alfa-2b (*Intron A*) plus ribavirin therapy is the standard initial treatment for patients with chronic hepatitis C, but a new report in *The Lancet* [2001;358:958-65] indicates that a peginterferon-based regimen achieves higher rates of sustained virological response (SVR). Previous studies have shown that peginterferon achieves SVR rates that are twice that of

standard interferon, but relapse rates are high with monotherapy, and most patients with genotype 1 infection, the most common form of infection and the most difficult to treat, do not achieve SVR.

In the new study, researchers investigated the effects of peginterferon alfa-2b combined with ribavirin

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NEW DRUGS AND INDICATIONS (continued)

Peginterferon Regimen for Chronic Hepatitis C (continued)

on viral suppression in 1530 patients with chronic infection. Patients were randomized to interferon subcutaneously three times a week or to one of two doses of peginterferon once a week. They also received a fixed daily dose of ribavirin. Twenty-four weeks after the 48-week treatment period, patients' serum was analyzed for the presence of hepatitis C virus (HCV) RNA.

The group that received the higher dose of peginterferon had an SVR rate of 54%, significantly higher than the 47% rate found in each of the other groups. The benefits of the higher dose were most apparent for patients infected with the HCV genotype 1. The corresponding SVR rates for these patients were

42% in the higher dose peginterferon group, 34% in the lower dose peginterferon group, and 33% in the standard interferon group. The rate for patients with genotype 2 and 3 infections was about 80% for all treatment groups. Further analysis suggested that the SVR rate associated with the higher dose of peginterferon might have been still higher if ribavirin had been dosed according to body weight. The lead investigators predicted that peginterferon plus ribavirin would become the standard treatment for chronic hepatitis C. Not only is it more effective than standard interferon therapy, but it is also given just once a week rather than three times a week [*Reuters Health*, 21 September 2001].

DRUG SAFETY

FDA Tightens Measures to Prevent Pregnancy in *Accutane* Users

The FDA reported that it has approved significant changes to Hoffmann-La Roche's pregnancy prevention program for the acne drug *Accutane* (isotretinoin). The program was adopted in 1988, when isotretinoin was conclusively linked to birth defects. But in recent years, the number of women becoming pregnant while on the drug may have actually increased because of more prescribing. The new restrictions will include requiring women to take a pregnancy test every month and permitting pharmacists to dispense only a one-month supply of *Accutane*. Physicians wishing to prescribe the drug will receive yellow "Accutane Qualification Stickers" that must be placed on the prescription to verify that the patient has had a negative pregnancy test and received birth control counseling. Furthermore, FDA will commission independent audits to ensure the enhanced program is working [*Reuters Health*, 1 November 2001].

Remicade "Dear Doctor" Letter Warns Against Use in Congestive Heart Failure

Remicade (infliximab) is approved for the treatment of Crohn's disease and rheumatoid arthri-

tis. Suppression of tumor necrosis factor (TNF) might also prove beneficial in the treatment of congestive heart failure (CHF). However, on learning that preliminary results of a phase II study investigating infliximab's use in CHF patients suggested that it could actually worsen the condition and increase hospitalization and mortality, Centocor placed further development on hold and sent out a "Dear Doctor" letter to alert physicians to the latest data. The letter says that *Remicade* should not be initiated in patients with Crohn's disease or rheumatoid arthritis who also have heart failure. In such patients already receiving *Remicade*, the letter advises that discontinuation be considered, especially if no significant clinical response is seen. Treatment must be stopped if CHF worsens. In March, Immunex also stopped a phase II/III trial of its TNF-blocker *Enbrel* (etanercept) in CHF after an interim analysis by the data monitoring board indicated that the trial would not reach the primary efficacy end point. The latest reports suggest that this may be the end of the road for TNF- α inhibitors in this indication [*Scrip*, 26 October 2001]. Safety issues in patients with CHF are the second setback for *Remicade*. Earlier, the FDA notified health professionals that sometimes-fatal tuberculosis and other serious opportunistic infections have been reported in patients treated with infliximab [*Reuters Health*, 24 October 2001].

DRUG SAFETY (continued)

Adverse Events Associated with Potent Antiretroviral Therapy

Only limited information is available about prevalence and severity of adverse events associated with highly active antiretroviral therapy in routine clinical practice. To learn more, investigators conducted a cross-sectional observational study of 1160 patients who were receiving potent antiretroviral treatment. They found that 47% of patients presented with clinical and 27% with laboratory adverse events probably or definitely attributed to antiretroviral therapy. Single-protease-inhibitor and protease-inhibitor-sparing regimens were associated with a comparable prevalence of adverse events. Compared with single-protease-inhibitor treatment, use of two protease inhibitors or a drug combination from three different classes was associated with higher prevalence of adverse events (odds ratios 2.0 and 3.9, respectively). The investigators also found that only abacavir was significantly associated with vomiting. Diarrhea was a side effect of all protease inhibitors except indinavir. Lamivudine and efavirenz use was correlated with a significant increased prevalence of mood disorders. The odds ratio of kidney stones associated with indinavir was 11.3. The nucleoside reverse transcriptase inhibitors lamivudine and stavudine were significantly associated with lipodystrophy. The investigators found no link between antiretroviral therapy and anemia. Creatine phosphokinase was significantly elevated in pa-

tients taking stavudine or abacavir, and stavudine and didanosine were linked with increased urate levels [*Lancet* 2001;358:1322-27].

Avandia May Increase Risk of Heart Failure

There is concern about the increased risk of congestive heart failure (CHF) in patients taking *Avandia* (rosiglitazone), especially when it is used with insulin. In fact, after reviewing a supplemental New Drug Application seeking an indication for combination use of rosiglitazone and insulin, the FDA set aside the request and directed the manufacturer to add new warnings to *Avandia*'s label. The package insert now emphasizes that the use of *Avandia* in combination therapy with insulin is not indicated.

Glitazones can cause fluid retention, which can exacerbate or lead to CHF. The problem is intensified when glitazones are given with insulin. Patients with NYHA Class III and IV heart failure were excluded from clinical trials of both *Avandia* and *Actos* (pioglitazone). There is no evidence at this time that the use of *Actos* with insulin poses a special problem, and combination therapy has received FDA approval. Nevertheless, patients at risk for heart failure who use *Actos*, with or without insulin, or *Avandia* should be monitored for shortness of breath, weight gain, edema, and fatigue [*Prescriber's Letter* 2001;8(10):58].

CLINICAL PRACTICE

Glutamine May Ameliorate Chemotherapy-Induced Mucositis

According to the *Prescriber's Letter* [2001; 8(10):57], some oncologists are using the amino acid glutamine to reduce the severity of mucositis caused by chemotherapy. The rapidly dividing cells of the gastrointestinal tract are highly susceptible to the effects of many chemotherapeutic agents, and a recent placebo-controlled study assessed the protective effect of oral

glutamine (6 g three times a day) in 70 patients about to receive chemotherapy (5-fluorouracil) for the first time. 5-FU was given daily for five days. Glutamine was given for 15 consecutive days, starting five days before the initiation of chemotherapy. 5-FU depressed intestinal absorption and permeability in both the placebo and

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CLINICAL PRACTICE (continued)

Glutamine May Ameliorate Mucositis (continued)

glutamine groups, but the degree of impairment was significantly reduced in the glutamine group. The duration of diarrhea was also reduced in the glutamine group, but not significantly so [*Gut* 2001; 48:28-33].

The *Prescriber's Letter* staff cautions that while glutamine looks promising, many questions remain unanswered. The most effective dose and duration of treatment are unresolved. Much higher doses are probably necessary for prevention of diarrhea than

for prevention of mucositis. Patients receiving high-dose chemotherapy may also require higher doses. Starting glutamine before starting chemotherapy may be an important factor, especially in patients who are glutamine-depleted. Nevertheless, the newsletter concludes, "Glutamine prophylaxis, under the supervision of an oncologist, may be worth a try in patients who are otherwise unable to tolerate adequate doses of chemotherapy because of gastrointestinal side effects" [*Prescriber's Letter* 2001;8(10):57].

Frequency of Progression to Hypertension in Nonhypertensive Individuals

Nonhypertensive individuals with optimum (<120/< 80 mm Hg), normal (120-129/80-84 mm Hg), or high normal (130-139/85-89 mm Hg) blood pressure may progress to hypertension (>140/90 mm Hg) over time. Studying nearly 10,000 men and women without hypertension, at least 52 years old at baseline, investigators assessed the rate of progression to hypertension. They found that in those younger than 65 years, 5.3% of individuals with optimum blood pressure, 17.6% with normal blood pressure, and 37.3% with high normal blood pressure progressed to hypertension over

four years. Corresponding four-year progression rates for patients 65 years and older were 16.0%, 25.5%, and 49.5%. The likelihood of developing hypertension was increased an additional 20-30% among individuals who experienced a 5% weight gain. The findings support recommendations for monitoring individuals with high normal blood pressure once a year and emphasize the importance of weight control as a measure for primary prevention of hypertension [*Lancet* 2001;358:1682-86].

Management of Elderly Patients Hospitalized for Peptic Ulcer Disease

The peptic ulcer disease quality improvement project of the Health Care Financing Administration (now the Center for Medicare and Medicaid Services) sought to encourage compliance with the 1994 NIH Consensus Conference guidelines that recommend screening for *Helicobacter pylori* (and treatment of infection), as well as elimination, where possible, of NSAID use in patients with peptic ulcer disease. Investigators have now assessed changes in peptic ulcer disease management after adoption of the guidelines in a cohort of 4292 hospitalized Medicare beneficiaries with a diagnosis of peptic ulcer disease, drawn from five states, and the impact of the guidelines on rehospitalization for peptic ulcer disease in a cohort of 752 patients in Colorado [*JAMA* 2001;286:1985-93].

Screening for *H. pylori* infection in 1995 (baseline) and 1997 (remeasurement) showed a significant

increase in each of the five states (12%-19%). Treatment of *H. pylori* infection also increased in each state (9%-13%). Despite increased screening, detection of *H. pylori* was much less frequent than expected in every state (13%-24%) and did not increase in any state. Screening for and counseling about nonsteroidal anti-inflammatory drugs (NSAIDs) did not significantly increase overall or in any state. In the Colorado cohort, treatment for *H. pylori* was not associated with a reduction in rehospitalization. Counseling about NSAID use, on the other hand, was associated with a decrease in risk of rehospitalization for peptic ulcer disease (adjusted odds ratio, 0.47).

A related editorial emphasized that the "take-home message from this study should not be to withhold treatment for *H. pylori* infection but, rather, should be to avoid NSAID use in patients with peptic ulcer disease, especially the elderly" [*Ibid*, 2023-24].