

drug therapy topics supplement

A Timely Discussion of Contemporary Issues

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CLINICAL PRACTICE

Triptan Selection for the Treatment of Migraines

There are now six triptans on the market in the U.S., all of which are effective and well-tolerated medications for migraine treatment. The *Prescriber's Letter* [2002;9:2] recommends, in general, that physicians initiate treatment with *Maxalt* (rizatriptan) or *Axert* (almotriptan) and then make changes depending on whether the patient needs a medication with a faster onset, longer duration of action, or fewer side effects. Rizatriptan tends to be faster acting than sumatriptan (*Imitrex*), the standard, and more effective, with a similar incidence of adverse effects. Almotriptan, approved only last year, seems to work about as well as sumatriptan, but it is better tolerated. Almotriptan may also be slightly better than sumatriptan for sustained relief. For patients started on *Maxalt* or *Axert* who require faster pain relief, physicians should consider intranasal or injectable *Imitrex*. For those who complain of side effects on *Maxalt*, one should consider prescribing *Axert*. Although there is little information on and only limited experience with *Frova* (frovatriptan), the most recently approved triptan, with a 26-hour half-life, it may have the lowest rate of headache recurrence at 24 hours after treatment.

Intermittent Highly Active Antiretroviral Therapy (HAART) Effective and Safer

Intermittent antiretroviral therapy for HIV-infected patients has captured the imagination of the AIDS community because it could reduce drug toxicity and cost. Compelling evidence of effectiveness, however, has been elusive. Now NIH researchers report the results of a pilot study in which 10 patients with levels of HIV RNA < 50 copies per ml of plasma and CD4 T cells counts > 300 cells per mm³ of whole blood received cycles of seven days on HAART and seven days off. They found in eight patients who completed the study that short-cycle intermittent HAART over 32-68 weeks maintained suppression of plasma viremia and HIV replication in reservoir sites while preserving CD4 T-cell counts. There was no evidence for the development of resistance to HAART medications. Notably, there was also a decrease in serum cholesterol and triglyceride levels. High cholesterol and triglyceride levels, along with a shift in body fat deposits, are major side effects of HIV therapy, collectively called lipodystrophy. This proof-of-concept study demonstrated the feasibility of reducing the amount of antiretroviral therapy by 50% while maintaining suppression of HIV in peripheral blood and lymphoid tissue, preserving CD4 T-cell counts, and reducing markers of toxicity [*Proc Natl Acad Sci USA* 2002;98(26):15161-66].

CLINICAL PRACTICE (continued)**Initiating Antiretroviral Therapy**

For many patients with chronic, asymptomatic HIV infection who have not received therapy, it is unclear whether such treatment should be initiated immediately to preserve HIV-specific CD4 T-lymphocyte cells or deferred until the CD4 count is lower and/or the plasma viral load is higher, to avoid the risk of toxicity. Now, a study has found that delaying antiretroviral therapy may not lead to poorer virological outcomes. A low CD4 count and a high viral load at baseline were not linked to poorer control of viral load [*JAMA* 2001;286:2560-67]. A second study in the same issue of the journal reports that baseline CD4 cell count, but not viral load, is predictive of disease progression to AIDS or death in HIV-infected patients who delay antiretroviral therapy [*Ibid*, 2568-77].

In the first report, investigators collected data on 3226 treatment-naïve HIV-infected patients who had known viral loads and CD4 counts before treatment. All started antiretroviral therapy with at least three drugs. At 32 weeks, 85% of the patients had a drop in viral load to fewer than 500 copies/ml. Regardless of baseline CD4 T-lymphocyte count or plasma viral HIV RNA level, there was no difference in achieving this low level of viremia. Subsequent rebound above 500 copies/ml was no more likely with a lower baseline CD4 cell count or higher viral load. However, a baseline

plasma viral RNA level of greater than 100,000 copies/ml did yield a slower rate of viral suppression after starting treatment. The lead author of the report told *Reuters Health* [28 November 2001], “Delaying therapy means avoidance of toxicity and inconvenience of drug-taking for a period of time.”

In the second report, researchers conducted a population-based study of 1219 treatment-naïve HIV-infected individuals to determine rates of disease progression stratified by baseline CD4 T-lymphocyte count and plasma HIV RNA level prior to initiating highly active antiretroviral therapy (HAART). Patients with CD4 counts of less than 50 copies/ml and those with counts of 50 to 199 copies/ml were 6.67 and 3.41 times more likely to die than patients with CD4 T-cell counts of 200 copies/ml or greater. The CD4 count was the only independent predictive indicator for progression to AIDS or death. An editorial on this study cautions that the recommendation to delay treatment until the CD4 T-lymphocyte count approaches 200 copies/ml is not appropriate for patients evaluated within six months of primary HIV seroconversion. “For those patients, immediate initiation of HAART may preserve HIV-specific T-helper cell function” [*JAMA* 2001; 286:2597-99].

Guidelines for Acute Coronary Syndrome without ST Elevation

Acute coronary syndrome—unstable angina and myocardial infarction (MI) without ST-segment elevation—are recognized as among the most frequent and important clinical manifestations of coronary artery disease, representing a volatile and dangerous intermediate stage between stable angina and ST-elevation MI or sudden death. In 2000, professional societies in Europe and the U.S. released guidelines on diagnosis, risk stratification, and treatment of these disorders. The guidelines summarize

current evidence and its application to clinical practice.

The most important recommendations relate to the inclusion of troponins into the risk stratification algorithm, the addition of low-molecular-weight heparins and glycoprotein IIb/IIIa antagonists to medical treatment, and the role of invasive management for improved long-term outcome [*N Engl J Med* 2002;346:206-208].

NEW DRUGS AND INDICATIONS

FDA Approves Tenofovir for Combination Therapy of HIV Infection

Gilead Sciences announced that it has received FDA approval to market *Viread*, a prodrug of tenofovir, for treatment of HIV infection in combination with other antiretroviral agents in previously treated patients. *Viread* is the first acyclic nucleotide analogue reverse transcriptase inhibitor to receive approval. Experts say that it may offer an important treatment option for HIV-infected patients in whom the virus has become resistant to currently available agents. Common side effects are nausea, diarrhea, vomiting, and flatulence. Gilead also said that it was conducting additional studies to evaluate *Viread* in combination with other agents for treatment-naïve patients and for children [*Reuters Health*, 30 October 2001].

Metformin Safe and Effective for Children with Type 2 Diabetes

A report in *Diabetes Care* [2002;25:89-94] concludes that the oral antidiabetic agent metformin is as effective and well tolerated in children as it is

in adults. This is useful new information in light of the markedly increased prevalence of type 2 diabetes in American children.

The investigators examined twice-daily doses up to 1000 mg per day in a well-controlled trial involving 82 children (ages 10 to 16 years) for up to 16 weeks. At baseline, the children had fasting plasma glucose between 126 mg/dl and 240 mg/dl; HbA1C was at least 7.0%. Metformin significantly improved glycemic control. Mean fasting plasma glucose fell by 43 mg/dl compared with a mean decline of 21 mg/dl in the placebo group. Metformin also significantly lowered HbA1C compared with placebo (7.5% vs. 8.6%).

Metformin improved fasting plasma glucose in both male and female children and in all racial subgroups, without a negative impact on body weight or lipid profile. Adverse events associated with metformin were abdominal pain, diarrhea, nausea and vomiting, and headache. About 15% of patients in the metformin group discontinued treatment compared with 10% in the placebo group.

DRUG SAFETY

Irinotecan Plus 5-FU Passes Adverse Drug Reaction Review

A large clinical trial showed the superiority of the chemotherapy combination of irinotecan (*Camptosar*), fluorouracil, and leucovorin (IFL) over irinotecan alone or fluorouracil and leucovorin in the initial treatment of metastatic colorectal cancer [*N Engl J Med* 2000;343:905-14]. The trial also demonstrated that the three-drug combination was not associated with a significantly increased incidence of toxicity as compared with the two other treatments. Subsequently, the FDA approved IFL as first-line therapy, and many oncologists adopted it as the standard of care. Last year, however, an urgent publication reported an unexpectedly high rate of death associated with the use of IFL in two separate clinical trials sponsored by the National Cancer Institute [*Ibid*, 2001;345:144-45].

In a comprehensive review of the safety of IFL, the FDA's advisory panel on oncologic drugs has unani-

mously accepted Pharmacia's argument that the reports of unexpectedly high early death rates attributed to IFL were not sufficient reason to remove the bolus regimen from *Camptosar*'s label and only recommend the infusion regimen. The reports had led researchers at the National Cancer Institute to halt two colorectal cancer trials that involved the bolus regimen. Pharmacia argued persuasively that *Camptosar* adds no greater mortality risk to 5-FU/leucovorin alone. A factor weighing against eliminating the bolus regimen was that more than 95% of patients who receive *Camptosar* get the bolus regimen rather than the infusion regimen. The panel, however, did recommend one label change, suggesting that the dose of *Camptosar* be reduced until the patient is free of diarrhea for 24 hours before retreatment. Diarrhea is common in patients treated with irinotecan, and severe diarrhea contributes to mortality [*Scip*, 12 December 2001].

DRUG SAFETY (continued)

Safety of Influenza Vaccine in Adults and Children with Asthma

Outbreaks of influenza are associated with substantial adverse effects, especially among people who have chronic diseases such as asthma. Influenzavirus makes asthmatics more susceptible to bronchoconstriction and even prolonged declines in lung function. Only 10% of patients with asthma receive the influenza vaccine, as compared with 68% of the population that is older than 65 years, another group for which annual immunization is strongly urged. To investigate the safety of the inactivated trivalent split-virus influenza vaccine in adults and children with asthma, researchers conducted

a well-controlled, crossover trial in 2032 patients ranging in age from 3 to 64 years. They found that the frequency of exacerbations of asthma was similar in the two weeks after the influenza vaccination and the placebo injection and that exacerbation rates were similar in subgroups defined according to age, severity of asthma, and other factors. The investigators concluded, "Given the morbidity of influenza, all those with asthma should receive the vaccine annually" [*N Engl J Med* 2001;345:1529-36].

Sleepiness in Parkinson's Disease Not Specifically Linked to Dopamine Agonists

Daytime sleepiness is common among people with Parkinson's disease, but contrary to an earlier report, the problem does not appear to be related to any specific treatment. In 1999, researchers reported eight cases in which patients who were receiving the dopamine agonists pramipexole (*Mirapex*) and ropinirole (*Requip*) fell asleep while driving and had accidents. As a result, physicians were advised to tell patients on these drugs not to drive.

A recently reported survey of Parkinson's patients determined that more than half of them acknowledged excessive daytime sleepiness, including half of those who drove. But there was no clear relationship between type of medication taken and scores on sleep questionnaires. Among drivers, 12% said they had dozed while driving; medication regimens varied widely. For example, 43 of 49 were taking levodopa. Eleven patients

were taking pramipexole, and 18 were receiving ropinirole. The rest were taking levodopa alone or with other drugs. Fewer than 4% of drivers said they had ever suddenly fallen asleep at the wheel. Only three of the 21 patients reporting sudden-onset sleep claimed to have no warning signs. In one case, the patient was taking pramipexole and pergolide, and in another the patient was taking ropinirole. In the third case, the patient was taking levodopa and pergolide [*JAMA* 2002;287:455-63].

The authors of the report say that it may be possible to identify Parkinson's patients at risk for motor accidents by routinely asking them about daytime sleepiness. Patients thought to be at risk for falling asleep behind the wheel should be cautioned to avoid driving regardless of drug treatment.

DRUG EVALUATION

Aspirin, Warfarin Equivalent for Prevention of Recurrent Ischemic Stroke

Despite the use of antiplatelet agents, usually aspirin, in patients who have had an ischemic stroke, there is still a substantial rate of recurrence. This prompted investigators to study whether warfarin, which is effective and superior to aspirin in the prevention of embolism in patients with atrial fibrillation, would also be superior in the prevention of recurrent ischemic stroke in patients with no history of atrial fibrillation. They enrolled 2206 patients who received warfarin (at a dose adjusted to produce an international normalized ratio of

1.4 to 2.8) or aspirin (325 mg/day) after they had experienced a noncardiogenic stroke. Most patients were followed for two years.

There was no significant difference between the treatment groups in the primary end point of death or recurrent ischemic stroke, which was reached by 17.8% of patients assigned to warfarin and 16.0% of people assigned to aspirin. The rates of major hemorrhage were low (1.22% in the warfarin group and 1.49% in

(Continued on Supplement page 5)

Aspirin, Warfarin Equivalent for Ischemic Stroke Prevention (continued)

the aspirin group), but patients assigned to warfarin experienced more minor bleeding than did patients assigned to aspirin [*N Engl J Med* 2001;345:1444-51]. Warfarin offered no additional benefit over aspirin. Aspirin, either alone or in combination with another

antiplatelet agent, appears to be a well-justified choice for the prevention of recurrent ischemic stroke. A related editorial adds that there is no evidence from clinical trials to support the use of oral anticoagulant therapy in this situation [*Ibid*, 1493-95].

Risperidone Bests Haloperidol in Preventing Relapse in Schizophrenics

As reported in the 3 January issue of *The New England Journal of Medicine* [2002;346:16-22], 356 clinically stable patients with schizophrenia or schizoaffective disorder were randomly assigned treatment with haloperidol or risperidone. Mean modal doses were risperidone 4.9 mg and haloperidol 11.7 mg. Median duration of treatment was 364 days in the risperidone group and 283 days in the haloperidol group.

By the end of the study, the investigators found that 39.9% of haloperidol-treated patients and 25.4% of risperidone-treated patients had relapsed. Patients who

received risperidone also scored significantly better at the end of the study on the Positive and Negative Syndrome Scale, whereas symptoms did not improve over baseline among those who used haloperidol. Extrapyramidal symptoms increased in severity in those assigned to haloperidol, but decreased in the risperidone group.

The principal investigators told *Reuters Health* [4 January 2002], "Relapse is without a doubt the worst event that can occur. The patient starts back at square one, is often hospitalized, becomes a danger to himself or others, and is unable to work or attend school for weeks or months afterwards."

Lowering Plasma Homocysteine Levels Decreases Coronary Restenosis

Restenosis after coronary angioplasty remains an important limitation of that intervention. Plasma homocysteine levels may play a role in the incidence of restenosis. Investigators recently reported that patients with homocysteine levels below 9 $\mu\text{mol/l}$ have a 49% lower rate of restenosis than patients with higher levels. Total plasma homocysteine level is a predictor of cardiovascular risk and correlates with the severity of coronary disease. Homocysteine levels can be reliably lowered with a daily dose of folic acid in combination with vitamin B₁₂ and pyridoxine. Hypothesizing that lowering of homocysteine levels would decrease the rate of restenosis after coronary angioplasty, investigators randomly assigned 205 patients to folate treatment or placebo for six months

after successful coronary angioplasty [*N Engl J Med* 2001;345:1593-600].

The multinational research team found that folate treatment significantly lowered plasma homocysteine from a mean of 11.1 $\mu\text{mol/l}$ to a mean of 7.2 $\mu\text{mol/l}$. At follow-up, the minimal lumen diameter was significantly larger in the group assigned to folate treatment, and the degree of stenosis was less severe. The rate of restenosis was also significantly lower in patients assigned to folate treatment (19.6% vs. 37.6%), as was the need for revascularization of the target lesion (10.8% vs. 22.3%). The authors of the report concluded, "This inexpensive treatment which has minimal side effects should be considered as adjunctive therapy for patients undergoing coronary angioplasty" [*Ibid*].

Dietary Supplements May Provide Effective Treatment for Macular Degeneration

A new study suggests that high doses of certain dietary supplements are effective in the treatment of macular degeneration, a condition that destroys the central portion of the retina and is the leading cause of vision loss among the elderly. The supplements—a combination of zinc, vitamin C, vitamin E, and beta-carotene—did not appear to slow the early stages of the disease or the formation of cataracts. But among those whose disease progressed to an intermediate stage, the

combination of zinc and the antioxidants reduced risk of disease progression by 19% [*Archives of Ophthalmology*, October 2001]. The daily dosages of the antioxidants used in the study were vitamin C 500 mg, vitamin E 400 mg, and beta-carotene 15 mg. The daily dosage of zinc was 80 mg, combined with copper 2 mg to avoid deficiency. These amounts are well above the usual levels recommended by nutritionists.

DRUG INTERACTIONS

Ibuprofen Prevents Platelet Inhibition by Aspirin

Ibuprofen may counteract aspirin's cardio-protective effects [*N Engl J Med* 2001;345:1809-17]. This adverse interaction has been suggested by investigators who conducted a six-day crossover study with single daily doses of aspirin 81 mg in combination with ibuprofen 400 mg, acetaminophen 1000 mg, or rofecoxib (*Vioxx*) 25 mg. Each treatment combination involved five subjects. Measurements of serum thromboxane B-2 were used to assess platelet cyclooxygenase-1 activity.

When aspirin was given two hours before ibuprofen, acetaminophen, or rofecoxib, thromboxane B-2 activity was almost completely inhibited for up to 24 hours after dosing. However, when ibuprofen was given two hours before aspirin, inhibition of thromboxane B-2 activity fell to only 54% by 24

hours after the dose. Pretreatment with acetaminophen or with rofecoxib did not alter aspirin's anti-platelet effect.

The researchers also conducted a parallel-group study in which subjects took aspirin before the first of three daily doses of ibuprofen or two daily doses of diclofenac (*Voltaren*) 75 mg. They found that the effects of low-dose aspirin on platelets were blocked by three doses of ibuprofen, but not by two doses of diclofenac, even when aspirin was given first. The investigators concluded, "The concomitant administration of ibuprofen but not rofecoxib, acetaminophen, or diclofenac antagonizes irreversible platelet inhibition induced by aspirin. Treatment with ibuprofen in patients with increased cardiovascular risk may limit the cardioprotective effects of aspirin" [*Ibid*].

CONTROVERSIES AND DILEMMAS

CDC Offers Advice on Childhood Vaccine Shortages

A continuing shortage of the pneumococcal conjugate vaccine (*Prevnar*) has prompted the Centers for Disease Control and Prevention to recommend that some doses be deferred until supplies return to normal. The vaccine became back-ordered in 2001 because of production limitations and an unexpected demand. In August 2001, the shortage worsened when production problems at Wyeth's manufacturing sites halted distribution for several weeks. These problems are now resolved. The company hopes to eliminate the bottleneck for *Prevnar* by the second quarter of 2002.

The recommended schedule for *Prevnar* is for three doses every two months in newborns, followed by a booster dose at 12-15 months. This remains in place for high-risk children. But on 14 September 2001, the CDC's Advisory Committee on Immunization Practices advised that booster doses for healthy children who have completed the primary series might be deferred. On 7 December, the committee voted to explicitly urge physicians to defer the fourth dose and to decrease their ordering for this vaccine to make dis-

tribution across the country more uniform [*The Pink Sheet*, 17 December 2001].

The CDC is proposing a similar strategy to deal with the shortage of the combination diphtheria-tetanus-pertussis vaccine, which started in 2000 when Wyeth Lederle and Baxter Hyland discontinued production, leaving only GlaxoSmithKline and Aventis Pasteur to fill the gap.

Infants ordinarily receive the first three doses of the vaccine at ages 2, 4, and 6 months, with a fourth dose given at 15 to 18 months, and a final dose given as the child reaches 4 to 6 years old. To ensure enough vaccine for infants, the CDC advises physicians to postpone vaccinating children between the ages of 15 and 18 months. The agency further recommends that if deferring the fourth dose does not leave a supply adequate to vaccinate all infants, then the fifth dose should also be deferred. The CDC cautions, however, that children traveling to countries where the risk of diphtheria is high should get the complete series of immunizations [*Reuters Health*, 7 January 2002].