AMERICAN HEALTH CONSULTANTS

The Physician's

Therapeutics & Drug Alert™

Volume 6, Number 4 Pages 25-32 november 2001

INSIDE

Statins Prove Effective in Decreasing Incidence of Alzheimer's Disease

By William T. Elliott, MD, FACP

Statins appear to decrease the incidence of alzheimer's disease (AD) according to 2 recent retrospective studies from Germany. Statins have been shown to cross the blood-brain barrier and inhibit de novo cholesterol synthesis in the brain. This may explain why statins appear to be more effective in preventing AD than other types of cholesterol-lowering medications such as **fibrates**, **resin binders**, or **nicotinic acid**, which do not cross the blood-brain barrier. Statins may reduce endogenous cholesterol in the brain, but they also seem to modulate the deposition of **A-beta-amyloid peptide** which is believed to be an early step in the development of fibril formation. This study raises intriguing questions, which need to be further studied, according to Simons and colleagues (Simons M, et al. *Neurology*. 2001;57:1089-1093).

Antibiotics

Pneumococcal resistance to **macrolide antibiotics** including **erythromycin**, **clarithromycin**, and **azithromycin**, nearly doubled between 1995 and 1999 according to a report from the CDC. In 1995, 10.6% of isolates were fully resistant to macrolides, with the percentage increasing to 20.4% by 1999. This occurred as macrolide use increased, especially among children. Currently, many treatment guidelines recommend macrolides as first-line agents for community-acquired pneumonia. Hyde and associates suggest that other agents may now need to be considered first line (Hyde TB, et al. *JAMA*. 2001;286:1857-1862).

"First generation" antibiotics **amoxicllin**, erythromycin, and **trimethoprim-sulfamethoxazole** are as effective as newer antibiotics at treating **acute sinusitis** according to a new study. The patient data were drawn retrospectively from more than 29,000 HMO patients. Nearly 60% received a first-generation antibiotic for a diagnosis of sinusitis while 40% received 1 of 14 "second-generation" antibiotics, generally broad-spectrum antibiotics such as second- or third-generation **cephalosporins** or **extended-spectrum penicillins**. Regardless of the drug chosen, the success rate was just over 90% after 28 days. The only significant difference was the cost of care, being significantly higher with second-generation antibiotics (Piccirillo JF, et al. *JAMA*. 2001;286:1849-1856).

Hypertension

Reduction of **blood pressure**, regardless of the antihypertensive agent chosen, is

the most important factor in reducing the risk of cardiovascular events. Staessen and colleagues, in this large meta-analysis of 9 clinical trials involving more than 62,000 patients, sought to establish whether certain antihypertensive agents had cardioprotective properties beyond their blood pressure lowering effects. **Calcium channel blockers** were found to offer more reduction in the risk of stroke, but less effective at reducing the risk of myocardial infarction. Otherwise, all antihypertensive agents including older agents such as **diuretics** and **beta blockers** offered the same benefit as newer agents such as calcium channel blockers and **ACE inhibitors**, and the newer agents offered no benefit beyond their blood pressure lowering effect (Staessen JA, et al. *Lancet.* 2001;358:1305-1310).

Anthrax

The recent anthrax exposures and illnesses have made "**Cipro**" a household word, creating more name recognition than the marketing department at Bayer could ever conceive. Although **penicillin** and **doxycycline** are also approved for the treatment of anthrax, "Cipro" has been getting all the press. Now Johnson and Johnson, the makers of **levofloxacin** (Levaquin) are seeking an indication for the treatment of anthrax also. The company has supplied the FDA with in vitro data showing activity against anthrax, as well as data demonstrating superior lung penetration compared to other quinolones. To its credit, Johnson and Johnson is prepared to donate 100 million tablets of levofloxacin to the government for dispersal to the general population should it become necessary. Meanwhile GlaxoSmithKline, which makes **amoxicillin** and Augmentin, says they are ready to ramp up production of their antibiotics if they should be needed. Neither drug has an indication to treat anthrax, but the company says both drugs are very effective against *Bacillus anthracis.*

Estrogen Replacement

Estrogen replacement has been found to be ineffective in the role of secondary prevention after myocardial infarction. (*Please see article on page 30*). Now a new study shows that estrogen replacement is similarly ineffective for secondary prevention of stroke. A randomized, double blind, placebo-controlled trial was done on 664 women who had suffered a stroke or TIA. They were randomized to 1 mg/d of **estradiol** or placebo. After a mean follow-up of 2.8 years there were 99 strokes or deaths in the estradiol group and 93 in the placebo group. The risk of death, rate of stroke, and the severity of nonfatal stroke were all worse in the estrogen group. Viscoli and associates conclude that estrogen replacement should not be prescribed for the secondary prevention of cerebrovascular disease (Viscoli CM, et al. *N Engl J Med.* 2001;345:1243-1249). ■

Ribavirin—A New Option for the Treatment of Hepatitis C

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda recently approved a "stand-alone package" of ribavirin capsules for the treatment of hepatitis C. Ribavirin is used in combination with interferon—either interferon alfa-2b or peginterferon alfa-2b. In 1998 the FDA approved a combination package of ribavirin and interferon alfa-2b that has been marketed under the trade name Rebetron. With the recent approval of a pegylated interferon alpha (PEG-Intron, Schering) and another on the way (Pegasys-Roche), ribavirin as a stand-alone product allows the flexibility to use these drugs in combination.

Indication

Ribavirin is indicated for use in combination with interferon alfa-2b (Intron A) for the treatment of chronic hepatitis C in adult patients with compensated liver disease previously untreated with alpha interferon or who have relapse after interferon therapy.[1] It is also indicated in combination with peginterferon alfa-2b (PEG-Intron) for the treatment of chronic hepatitis C in patients with compensated liver disease who are naïve to interferon alpha therapy.[2]

Dosage

The recommended dose of ribavirin with interferon alfa-2b is based on body weight. For patients < 75 kg the dose is 400 mg (2 ´ 200 mg) in the am and 600 mg (3 ´ 200 mg) in the pm. For patients > 75 kg, the dose is 600 mg (3 ´ 200 mg) in the am and pm. This is administered with 3 million IU of interferon alfa-2b (Intron A) 3 times weekly. In patients with a history of stable cardiovascular disease, a permanent dose reduction is needed if the hemoglobin decreases by 2 g/dL or greater during any 4-week period. Ribavirin should be discontinued if the hemoglobin remains below 12 g/dL after 4 weeks of a reduced dose. In patients with no cardiac history, the dose should be reduced to 600 mg daily (200 mg am and 400 mg pm) if hemoglobin falls below 10 g/dL and discontinued if it falls below 8.5 mg/dL.[1]

In combination with peginterferon (1.5 mg/kg/wk), the recommended dose is 800 mg in 2 divided doses (with breakfast and dinner). If hemoglobin drops below 10 mg/dL, but not below 8.5 mg/dL, the dose should be reduced by 200 mg/d.[2] In those with a history of stable cardiovascular disease, the dose of peginterferon should be reduced by half and the dose of ribavirin by 200 mg/d if the there is a > 2 g/dL decrease in hemoglobin in any 4-week period, and discontinued if Hgb is < 12 g/dL. Ribavirin should be discontinued if there is significant decrease in WBC, neutrophils, or platelets.[2]

Treatment is generally 24-48 weeks for treatment-naïve patients and 24 weeks for treatment-relapse patients.

Ribavirin is supplied as 200-mg capsules in packages of 84. The bottles should be stored at 25°C or 77°F.

Potential Advantages

The approval of the "stand alone" ribavirin provides more dosing flexibility in tailoring individualized therapy for those patients requiring dosage reduction as well as allowing use with peginterferon. In the clinical trials, about 26% of patients required modification in the dose of ribavirin. These included dose reduction or discontinuation. The combination package (Rebetron) contains a week's supply of ribavirin (35 or 42 capsules) and does not allow for the flexibility of dose reduction in patients with anemia associated with ribavirin therapy.

Potential Disadvantages

Ribavirin is not effective as monotherapy for hepatitis C. Hemolytic anemia, which occurs in about 10% of patients, is the primary adverse effect of ribavirin.[1] The drug can also potentiate the neutropenia induced by interferon alpha.[2] Ribavirin should not be used in pregnant patients or those with a creatinine clearance < 50 mg/min.

Comments

The combination of ribavirin and interferon alfa-2b has been approved for the treatment of patients who have relapsed following interferon alfa-2b therapy as well as those naïve to treatment. The combination has been reported to be more effective than interferon alone in both relapsing as well as naïve patients.[1,3,4,7] Ribavirin was recently approved for use in combination with peginterferon alfa-2b (PEG-intron) which is a conjugate of monomethoxy polyethylene glycol (PEG) with recombinant interferon alfa-2b. The pegylated interferon permits a more convenient once-weekly dosing. In interferon treatment-naïve patients, the combination of ribavirin (800 mg daily) plus peginterferon (1.5 µg/kg week) produced a better overall response (undetectable virus in the serum in 24 weeks) than ribavirin (1000 or 1200 mg) plus interferon 3 MIU 3 times a week (52% vs 46%, respectively). The difference was seen in genotype 1 hepatitis C compared to genotypes 2-6.[2,6] A recent report of a 24-week interim analysis suggests that ribavirin/peginterferon may be effective in patients who have previously failed on other interferon therapy.[5]

Clinical Implications

It is estimated that about 4 million Americans are chronically infected with hepatitis C and it is the leading reason for liver transplantation in this country. The combination of ribavirin and interferon is currently considered the standard of care. The approval of "stand alone"ribavirin permits its use with peginterferon and also allows for more flexibility in dosage modification due to adverse effects. As more data are published, peginterferon may become the standard interferon. Schering has agreed to conduct several postmarketing studies including the comparison of weight-adjusted doses of ribavirin with the currently approved fixed dose which is underway. Data suggest that body weight is an important predictor of response to interferon.[6] Rebetol is expected to be available in November and a combination PEG-Intron/Rebetol product is also pending. ■

References

1. Rebetol Product Information. Schering Corporation. July 2001.
2. PEG-Intron Product Information. Schering Corporation. August 2001.
3. Mereno-Monteagudo, et al. *Aliment Pharmacol Ther.* 1998;12(8):717-723.
4. Reichard O, et al. *Lancet.* 1998;351:83-87.
5. Jacobson I, et al. *Digestive Disease Week* 2001. May 20-23, 2001. Atlanta, GA. Abstract #1964.
6. Manns MP, et al. *Lancet.* 2001;358:958-965.
7. Poynard T, et al. *Lancet.* 1998;352:1426-1432.

Tramadol/Acetaminophen Tablets

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

The fda recently approved a combination of tramadol and acetaminophen for the short-term management of acute pain. Acetaminophen (APAP), which has long been added to narcotic pain releivers to

potentiate their effect, is added to tramadol (Ultram) for the same purpose. The combination, marketed as Ultracet, has a faster onset of action than tramadol alone and longer duration of analgesia than tramadol or acetaminophen alone.

Indications

Tramadol/APAP is indicated for the short-term (5 days or less) management of acute pain.[1]

Dose

The recommended dose is 2 tablets every 4-6 hours as needed for pain relief. The maximum dose is 8 tablets per day. The dose should not exceed 2 tablets every 12 hours in patients with impaired renal function (creatinine clearance < 30 mL/min).[1] Tramadol should not be used in situations where opioids are contraindicated and should not be used in pregnant women prior to or during labor. Chronic use during pregnancy is also not advised. Tramadol/APAP should be used at a reduced dose and with caution in patients taking other CNS depressants.[1]

Ultracet is supplied as tablets containing 37.5 mg of tramadol and 325 mg of acetaminophen.

Potential Advantages

This combination has been reported to provide better pain relief and faster onset of action and a longer duration than equivalent single doses of either APAP or tramadol in oral surgical pain.[1] Ultracet is not scheduled.

Potential Disadvantages

Tramadol/APAP is only approved for use for 5 days or less.[1] Tramadol is less effective in orthopedic surgical pain than dental pain.[1] Seizures have been reported in patients taking tramadol and this risk may be increased with concomitant administration of selective serotonin reuptake inhibitors (SSRIs) antidepressants, tricyclic antidepressants (TCAs), or other chemically related drugs (eg, cyclobenzaprine, promethazine), other opioids, MAO inhibitors, neuroleptics, and drugs which may lower seizure thresholds.[1] The risk appears to be highest among those aged 25-54 years, with 4 or more prescriptions, and those with a history of alcohol abuse, stroke, or head injury.[4] Tramadol has the potential for inducing physical dependence of the opioid type although the incidence has been reported to be less than 1 per 100,000.[1,5] This was based on data collected as part of a postmarketing surveillance program. Abstinence syndrome has been reported and dose tapering may be considered.[7] Tramadol/APAP may impair mental and physical ability to drive or operate machinery and other drugs with similar effects could enhance these effects.

Comments

The intent of combination analgesics is to provide a synergistic action as well as facilitate prescribing. Combination analgesics may also improve compliance by reducing the total number of tablets a patient must take to manage pain. Tramadol is a synthetic, centrally acting analgesic with 2 different mechanisms. These include a opioid mechanism (binding to m-receptor) and a nonopioid mechanism involving reuptake of norepinephrine and serotonin.[3] It is less likely to cause respiratory depression, constipation, and dependence than narcotic analgesics. However, tramadol alone is not a high quality analgesic, it has been categorized by the World Health Organization as an analgesic of low quality and no better than codeine/APAP.[6] The addition of APAP to tramadol appears to result in synergistic analgesia in mice models and it appears to be addictive in humans.[1,2] In oral surgical pain, tramadol/APAP is a little less effective than hydrocodone/APAP on a tablet for tablet basis but more effective than tramadol or APAP alone.[1] Ultracet is priced at approximately $0.80 per tablet which is the same as tramadol (50 mg).

Clinical Implications

Tramadol/APAP provides a combination which appears to be more effective than tramadol or APAP alone in relieving pain. In patients in whom NSAIDs or narcotic analgesic combinations are not appropriate, particularly due to intolerance, tramadol/APAP may offer another option. However, its use is recommended for only 5 days or less. ■

References

1. Ultracet Product Information. Ortho-McNeil Pharmaceutical, Inc. August 2001.
2. Raffa RB. *J Clin Pharm Ther*. 2001;26(4):257-264.
3. Scott LJ, Perry CM. *Drugs*. 2000;60(1):139-176.
4. Gardner JS, et al. *Pharmacotherapy*. 2000;20(12): 1423-1431.
5. Cicero TJ, et al. *Drug Alcohol Depend*. 1999;57(1): 7-22.
6. *Prescrire Int*. 1998;7(33):9-12.
7. Freye E, Levy J. *Eur J Pain*. 2000;4(3):307-311.

Clopidogrel: Is it the Perfect CURE?

Source: *Mehta SR, et al. Lancet. 2001;358:527-533.*

The clopidogrel in unstable angina to prevent recurrent events study (CURE) was designed to be a trial of non-invasive medical management

of unstable angina.[1] A total of 12,562 patients without ST elevation on EKG and with symptoms suggestive of an acute coronary syndrome were randomly assigned to receive aspirin and either clopidogrel or placebo. Despite the emphasis on noninvasive management, 2658 of these patients required percutaneous coronary intervention (PCI) during their hospital stay (1730) or after discharge (928; median time to PCI = 49 days). Prior to the procedure, 1313 of these patients had been randomized to clopidogrel; 1345 of the patients had been randomized to placebo prior to the procedure. These patients were the subject of the retrospective PCI CURE study.

There was considerable overlap in treatment between the 2 groups. Twenty-five percent of each group was started on open-label thienopyridines (clopidogrel or ticlopidine) during the procedure. Eighty percent of both groups were continued on thienopyridines for a median of 30 days after the procedure. Thereafter, subjects were assigned to their study assignment, and followed for 6 months. The primary outcome was a composite score of cardiovascular death, myocardial infarction, or revascularization.

The risk of repeat myocardial infarction or ischemia prior to the procedure was lower in the clopidogrel group (relative risk [RR] = 0.76; confidence interval [CI] 0.62-0.93). Patients given clopidogrel also had a reduced risk of myocardial infarction at 30 days (RR = 0.56; CI 0.35-0.89) and at 8 months of follow-up (RR = 0.71; CI 0.51-0.99). There was not a significant difference in cardiovascular death or need for revascularization. The composite end point was lower in the clopidogrel group (RR = 0.69; CI 0.54-0.87). There was no difference in major bleeding.

Comment by Jeff Wiese, MD

This study supports prior studies suggesting that thienopyridines (clopidogrel or ticlopidine) have an additive benefit to aspirin in the medical management of acute coronary syndromes. Patients who received clopidogrel had a 30% reduction in the composite end point. This difference was almost completely due to a reduction in myocardial infarction. The absolute risk reduction was 3.8%; the number of patients needed to treat to prevent 1 myocardial infarction was 26. There was not a significant difference in mortality or need for revascularization.

The 2 groups were equal with respect to age, gender, diabetes, smoking status, prior MIs, EKG abnormalities, and stent placement. Nonetheless, the decision to perform the PCI was at the discretion of the individual physician, and not the study protocol. It is possible that the initial treatment assignment (clopidogrel or placebo) created a selection bias with respect to the need for revascularization.

The number of patients requiring revascularization was similar in both groups, but the time of revascularization was not. The clopidogrel group had a disproportionate number of PCIs occurring after discharge, while most of the interventions in the placebo group occurred during the initial hospitalization. It is possible that the interventions occurring after discharge were more likely to be elective, and may represent a different patient population.

It is impossible to determine the best time to administer clopidogrel from the results of this study. With the exception of the few days prior to the procedure, the 2 groups received essentially the same treatment (clopidogrel) for the first 30 days. Eighty percent of patients in both groups received thienopyridines between the intervention and the first 30 days. It is not clear if the initial assignment of clopidogrel at presentation, or the continuation of clopidogrel (from 30 days to 8 months) was responsible for the reduction in repeat myocardial infarction. A randomized trial would be required to determine this important question.

Eighty percent of all patients in this study received a coronary stent. The use of IIb/IIIa inhibitors, which is a common clinical practice in this clinical setting, was discouraged as part of the CURE protocol. This may limit this study's generalizability to current clinical practice. Although there is evidence to support the additive benefit of clopidogrel and IIb/IIIa inhibitors, this study cannot provide insight into the additional benefit of clopidogrel on top of an aspirin and IIb/IIIa inhibitor.[2,3] ■

References

1. Yusuf S, et al. *N Engl J Med*. 2001;345:494-502.
2. Cannon CP, et al. *N Engl J Med.* 2001;344:1879-1887.
3. Steinhubl SR, et al. *Circulation*. 2001;103:1403-1409.

Dr. Wiese is Chief of Medicine, Charity, and University Hospitals, Associate Chairman of Medicine, Tulane Health Sciences Center, New Orleans, La.

Itraconazole and Terbinafine May be Linked to Liver and Heart Failure

Source: *Thompson CA. Am J Health Syst Pharm. 2001;58:1076.*

Due to reports of serious adverse events during therapy with itraconazole (Sporonox, Janssen) and terbinafine (Lamisil, Novartis), the

Food and Drug Administration (FDA) has advised clinicians to prescribe these agents for onychomycosis only after a positive nail culture or smear has been obtained. The FDA took this action after reviewing 24 cases of liver failure that were possibly associated with itraconazole therapy and 16 cases of liver failure that were possibly associated with terbinafine therapy as well as a number of cases of congestive heart failure (CHF).[1] Some of the patients (number not specified) did not have any underlying liver disease prior to antifungal therapy and a combined total of 11 deaths were reported. In addition to liver failure, there were 58 patients that reportedly developed CHF as a result of itraconazole therapy with 13 deaths in that group. Onychomycosis was specifically targeted because more than half of the cases of liver failure associated with itraconazole therapy were patients being treated for nail or other dermatological infections.

As a result of this information, the black-box warning in the labeling for itraconazole products now includes instructions to avoid the use of itraconazole therapy in treatment of onychomycosis in patients with signs or symptoms of CHF, or other conditions involving ventricular dysfunction, and to stop therapy in those patients that develop any signs of CHF. Two other items were also added to the black-box for itraconazole. One is the contraindication to the concurrent use of the antiarrhythmic agent dofetilide and itraconazole because of the possibility of serious cardiovascular events and the other is a warning regarding the ability of erythromycin to increase plasma levels of itraconazole.

The new labeling for both products now advises clinicians to closely monitor patients for signs and symptoms of liver failure or CHF and to take appropriate actions should signs and symptoms occur.

Comment by Thomas G. Schleis, MS, RPh

Anyone who has been involved in medicine for any period of time has witnessed the rise and fall of a number of pharmaceuticals. It is often not until large numbers of patients have been treated with newer medications that rare, but serious side effects are identified. In the case of itraconazole, it also appears that the length of therapy was important as the longer the therapy, the higher the likelihood of adverse events. This could have been identified only after the drug had been on the market for a considerable period of time.

Another aspect touched on in this article was the potential of drug interactions of itraconazole with dofetilide and erythromycin. With the large number of drug interactions between medications, it is almost a necessity for physicians to have access to drug interaction information, either through their pharmacy or by using one of the many products available for hand-held devices. I would encourage all physicians to verify that their pharmacies are carefully screening all medication profiles for potential medication interactions. ■

Reference

1. FDA Talk Papers. http://www.fda.gov/opacom/hpwhats.html#press. Accessed September 27, 2001.

Dr. Schleis is Director of Pharmacy Services, Infections Limited, Tacoma, Wash.

Postmenopausal Hormone Use and Secondary Prevention of Coronary Events

Source: *Grodstein F, et al. Ann Intern Med. 2001;135:1-8.*

The heart and estrogen/progestin replacement Study (HERS) hypothesized that postmenopausal hormone use in women with established cardiovascular disease would reduce recurrence of cardiovascular events. In this study, 2763 women with active heart disease were randomized to either placebo or Prempro® and followed for 5 years. In the first year, the rate of recurrence was 52% higher in the hormone replacement therapy (HRT) arm. In the second year, there was no difference between arms. However, in the fourth and fifth years, the women assigned to hormone use had a 33% lower risk for coronary events. Grodstein and associates used the data from the Nurses' Health Study to examine the same hypothesis. Although the Nurses' Health Study is observational, the population size is large and the participants have been followed for up to 20 years. Thus, the relationship between postmenopausal hormone use and secondary prevention of cardiovascular disease was examined in 2489 women. Ascertainment of hormone use and cardiovascular events was rigorous and complete, with total follow-up exceeding 92%. Of the hormone users, 53% used oral conjugated estrogen alone, 19% used oral conjugated estrogen plus oral progestin, and 28% used other types, mostly transdermal or oral

estradiol. The overall age-adjusted relative risk (RR) for recurrent major coronary events was 0.56 (confidence interval [CI], 0.39-0.80) among current users as compared with never-users. When the duration of hormone use was examined, a 25% increase in the risk of recurrent cardiovascular events was found among women with less than 1 year of use, but this increase was statistically nonsignificant, RR = 1.25 (CI, 0.78-2.00), because only 24 of the 141 cases fell into this group. However, longer-term users experienced a statistically significant decreased risk of 0.38 (CI, 0.22-0.66).

Comment by Sarah L. Berga, MD

The popular press is now reporting that postmenopausal hormone use does not reduce the risk of cardiovascular disease. Although that statement is a gross oversimplification of the results of the HERS, it continues to sway opinion and practice. The sophistry is kept alive by the difficulty inherent in explaining to patients the difference between primary and secondary prevention. Further, while primary care clinicians and gynecologists generally see patients seeking primary prevention, cardiologists typically see them after the initial cardiovascular event. Thus, we tend to counsel very different subsets of women. Available data suggest that HRT is better for primary rather than secondary prevention and this has left most cardiologists feeling understandably disenchanted with the promise of HRT. Given these considerations, it becomes increasingly important for clinicians to be able to clearly articulate why it is too soon to discount HRT use by women with established or latent cardiovascular disease. Is HRT as potent a therapy as statins for women with CVD or at high risk for CVD? Probably not. But statins do not provide the panoply of benefits that accrue to long-term HRT use. It falls to us to explain to women that HRT use is but one of the strategies for promoting health as one ages, but an important one nonetheless. Is one form of HRT better than another in helping to retard the ill effects of aging or for use in women with active heart disease? There are few data on this point. Is HRT the only strategy one should recommend? Of course not. So much of remaining healthy comes from having a healthy lifestyle, and we should not fool ourselves or our patients that HRT can reverse or counter the damage that comes from obesity, smoking, inactivity, and the like. HRT is best seen as an adjunct to a healthy lifestyle and not as a magic bullet that erases established cardiovascular disease, but this does not mean that HRT is useless or without benefit. This is what our patients need to know.

The bimodal response to therapy, with increased risk of recurrent cardiovascular disease confined to the first year of use, is puzzling. Many explanations have been proffered. It would be nice to know the reason, because if we did, we might be able to do something in the first year of HRT use to reduce that risk. It has been widely hypothesized that the increased risk is due to enhanced coagulation and that this may be due to the hepatic first-pass effect of oral estrogen use. We do know that standard oral therapy increases the risk of thromboembolic events. Would this risk be obviated by transdermal estradiol use when the circulating estradiol level is titrated to the subphysiological range? The present study simply did not have sufficient power to address this hypothesis. ■

Dr. Berga is Professor and Director, Division of Reproductive Endocrinology and Infertility, University of Pittsburgh, Pittsburgh, Pa.

Treatment of Adults with Sore Throat by Community PCPs

Source: *Linder JA, Stafford RS. JAMA. 2001;286:1181-1186.*

Despite the fact that a diversity of suggested management plans for acute upper respiratory infections abounds, clinicians often use methods that reflect practice contrary to such guidance. Linder and Stafford propose that in cases of sore throat, the only bacteria that merits treatment is Group A beta-hemolytic streptococci (GABHS), for which first-line treatment recommendations generally include penicillin and erythromycin.

Linder and Stafford performed a retrospective analysis of 2244 adult primary care visits for sore throat over a 10-year period (1989-1999). Almost three-fourths of patients received antibiotic treatment, though it has been repeatedly demonstrated that the majority of adult pharyngitis cases are viral. Additionally, less than one-third of the antibiotic prescriptions were for penicillin or erythromycin.

Comment by Louis Kuritzky, MD

Over the 10-year study period, use of nonrecommended antibiotics actually increased. On the other hand, in the most recent year surveyed, overall antibiotic prescribing was reduced by almost one third, though there was no diminution of nonrecommended antibiotic use, most common of which was prescription of aminopenicillins.

They have demonstrated that community-based primary care physicians commonly overprescribe antibiotics, and often choose agents that are not traditionally recommended as first-line. ■

Therapeutics & Drug Brief

Recommendations for Smallpox Vaccination

Source: *MMWR Morb Mortal Wkly Rep. 2001;50:RR-10:1-25.*

The events of september 11 heightened concerns of a potential bioterrorist attack. Of the several agents of concern is smallpox (variola) virus, although experts believe that the probability of a deliberate attack using this agent is low. Physicians should be aware that, in the United States, the routine use of smallpox vaccine (vaccinia) in the general public stopped in 1971; vaccination of health care workers stopped in 1976; availability of vaccine to the public and to international travelers ceased in 1982; and the administration of vaccine to military personnel ended in 1990. Therefore, most people in the United States, with the exception of some military personnel, received vaccine more than 25-30 years ago, with the possible loss of protective immunity.

A new smallpox vaccine is currently being developed using cell-culture techniques (*Infectious Disease Alert.* 2000;20:24). At present, pre-exposure vaccination is not being recommended except for key military and laboratory personnel involved in this area of viral research. In the event of an outbreak, postexposure vaccine will be made available to persons who are directly exposed to a clinical case or who are likely to be exposed to contaminated medical waste and laundry. If at all possible, persons who received childhood vaccine (or who received vaccine > 3 years ago) should be revaccinated and assigned to direct patient care duties.

In the event of a suspected case, physicians in the United States should immediately contact their local and state health authorities, who will contact the CDC. (Physicians in countries outside the United States are to contact the World Health Organization). ■

The Therapeutics & Drug Brief was written by Carol A. Kemper, MD, FACP. Dr. Kemper is Clinical Associate Professor of Medicine, Stanford University, Division of Infectious Diseases; Santa Clara Valley Medical Center, Santa Clara, Calif.

CME questions

Testing form inserted in the January 2002 issue

10. Which one of the following is *not* true about ribavirin?

a. It is indicated for the treatment of hepatitis C only in combination with interferon.
b. Hemolytic anemia is the primary adverse reaction to the drug.
c. Data suggest that ribavirin/peg-interferon may have some benefits over ribavirin-interferon.
d. Treatment regimens are generally 12 weeks.

11. Which of the following best summarizes the results of the Grodstein et al study?

a. It replicated identically the HERS study.
b. The results are similar to those of the HERS in that there is a bimodal response with increasing duration of HRT use.
c. The results contradict those of the HERS and the methods are better, thus we can reject the HERS results.
d. The data are suspect because the duration of follow-up is so much shorter than that of the HERS.
e. Ascertainment bias appears to have confounded the study methodology and thus the results cannot be trusted.

12. Tramadol/APAP (Ultracet) should not be used for longer than 5 days.

a. True
b. False

Subscriber Information

Customer Service **1-800-688-2421**

E-mail: customerservice@ahcpub.com

Editorial E-Mail: robert.kimball@ahcpub.com

World-Wide Web: http://www.ahcpub.com

Internet CME: http://www.cmeweb.com

THOMSON AMERICAN HEALTH CONSULTANTS

The Physician's Therapeutics & Drug Alert,™ ISSN 1089-6538, is published monthly by American Health Consultants, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305. **Back issues: $33. Price:** $249 per year. **Canada:** Add GST and $30 shipping. GST Registration Number: R128870672. **Other International:** Add $30. **Multiple copies—**2-9 copies: $159 each; 10-20 copies: $119 each.

ACCREDITATION: American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours in Category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians. This CME activity was planned and produced in accordance with ACCME Essentials.

In order to reveal any potential bias in this publication, and in accordance with the ACCME, we disclose that Dr. Schleis is on the speaker's bureau for Roche, Aventis, and Bayer and is a consultant for FFF Enterprises, Aventis, and Bayer. Dr. Kemper serves on the speaker's bureau of Virologic, GlaxoSmithKline, Pfizer, and Agouron and is involved in research with Chiron, Merck, Agouron, and Virologic. Dr. Berga is a consultant for Parke-Davis, Organon, and Women First, Inc., and is involved in research for Berlex and Health Decisions, Inc. Dr. Kuritzky is a consultant for GlaxoSmithKline and is on the speaker's bureau of GlaxoSmithKline, 3-M, Wyeth-Ayerst, Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, Jones Pharma, and Boehringer Ingelheim. Drs. Chan, Elliott, and Wiese report no financial relationships with companies having ties to this field of study.